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Integrative actions of the reticular formation The reticular activating system, autonomic mechanisms and visceral control

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THE INTEGRATIVE ACTIONS OF THE RETICULAR FORMATION

The Reticular Activating System, Autonomic Mechanisms and Visceral Control

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INTRODUCTION

French 1960 (1, p. 1281) stresses the importance of the Reticular Formation (R.F.). "It now appears likely that the brain-stem reticular formation represents one of the more important integrating structures if not, indeed, the master control mechanism in the central nervous system." The R.F. in man is limited to the core of the brainstem from the medulla to the thalmus. The entire nervous system is R.F. if one proceeds down the phylogenetic scale to the level of Amphioxis (2). Brodal describes the R.F. as "diffuse aggregations of cells of different types and sizes, separated by a wealth of fibres travelling in all directions. Circumscribed groups of cells, such as the red nucleus or the facial nucleus, formed of relatively closely packed units of a more or less uniform size and type, are not considered to be part of the reticular formation, which forms, so to speak, a sort of matrix in which the 'specific' nuclei and the more conspicuous tracts, e.g., the medial longitudinal fasciculus, are imbedded." (3)

The R.F. receives afferents from every sensory modality via cranial nerves and the spinal cord; and the rhinencephalon, neocortex, and cerebellar structures;

each in several ways, projects to the R.F. (4). Important reticulofugal projections pass to the neocortex; rhinencephalon; cerebellum; and probably to sensory and motor pathways, and sensory receptors, of every modality (4,5). Most afferents to the R.F. are colaterals of discrete pathways, segmentally ramify, and show marked convergence (6,7). Centrifugal R.F. efferents utilize cranial nerves and the spinal cord. Nerve degeneration-staining studies show the reticulospinal tract to end largely at the thoracic level (7,4), but antidromic R.F. evoked potentials result from single lumbosacrol neuron stimulation (8) and multisynaptic funicular cord channels are utilized (4, etc.)

R.F. neurons show great size variability (9), form 98 morphologic nuclei (10), and all have long dendrites--each neuron probably synapsing with 4000 (.3% of) R.F. neurons (6). Intra-reticular conduction is both polysynaptic and direct, the latter over slowly conducting diffuse tracts (7,4). Temporal + humoral conduction parameters, as well as anatomy, determine specificity of reticular action (10,11,4).

In amplification of French's concise statement (above) of R.F. action Rossi and Zanchetti (4) list R.F.

functions. They include 1) visceral-autonomic regulation, 2) regulation of cortical-subcortical electrocortical and behavioral arousal, ~~and~~ 3) regulation of postural tonus and phasic motor activity, and 4) modification of nerve transmission and cerebellar action. The first two subjects will be discussed in this paper.

Reticular physiology is even broader than described in these four statements. Besides modifying synaptic transmission at probably every level of the nervous system (cortex, thalmus, spinal cord, ventral and dorsal root, sensory receptor, etc.), through R.F. action habituation of synaptic transmission is produced (5). Moreover, the R. F. plays a significant roll in the habituation of the arousal reaction, production of the orienting reflex (12), and in the early and possibly later stages of conditioning in general (13, 12). The brainstem "synchronizing center" is important in the production of Pavlovian sleep as well as in the genesis and modulation of sleep in general (15, 16).

Reticular physiology is assuming great importance in pharmacology, especially in understanding anesthetic, narcotic, autonomic, neurohumor, tranquilizer and psychomemetic drug action. Similarly, the physiology of decerebrate rigidity, and vestibular, basal gangliar,

cerebellar, and cortical neurophysiology has been clarified by understanding R.F. function. This has in turn led to important advances in the understanding of spasticity, paraplegia, akinetic mutism, tremor, epilepsy, narcolepsy, cheyne stokes respiration,and many other clinical entities which appear to have a basis in abnormal reticular physiology.

THE RETICULAR ACTIVATING SYSTEM

HISTORICAL REVIEW

The specific function of the bulbar, mesencephalic R.F. in producing electrocortical arousal and sleep was established; and the function of the R.F. in producing behavorial arousal, attention, and physiological sleep was strongly suggested by the classic experiments of Moruzzi and Magoun who presented their results in the Journal of Electroencephalography and Clinical Neurophysiology, 1949. Before a discussion of their results it is important to note, as did they, the results of numerous preceding investigations which shed light on the significance of the brain stem R.F..

Thirty years after the discovery of the E.E.G., Beck (1905)[1] first noted the disappearance of generalized high voltage E.E.G. activity by stimulation of any peripheral nerve. The breaking up of the synchronous (sleep) cortical discharge by afferent stimulation (by opening the eye lids) was first observed by Berger (1930), and was since found to be a common response to any type of afferent stimulus. Rheinberger and Jasper (1932), Ectors (1936), and Bremer (1943) noted that sensory stimulation regardless of the modality would activate the E.E.G. over cortical areas other than those receiving the afferent system stimulated. Adrian (1934) suggested that desynchronization (EEG arousal) was produced by

afferent volleys preventing cortical neurons from beating in phase. Although prominent coma does result from the removal of the cerebral cortex in man, Bard and Rioch (1937) showed that decorticated animals continued to exhibit periodic variations between relative wakefulness and sleep. Bremer (1935, 1938) made a fundamental discovery that the cerveau isolé animal (transection of the midbrain, including the midbrain R.F.) resulted in a cortical EEG pattern resembling that of sleep or that of barbiturate anesthesia. He suggested that this was accomplished by deafferentation of the cerebral cortex. Barris and Ranson (1936), Ranson (1939), and Magoun (1948) noted the failure of afferent stimuli in producing arousal in preparations with brainstem lesions not involving the major sensory paths.

In humans naturally occurring brainstem lesions not involving sensory tracts were shown to be associated with somnolence by Fulton and Baily (1929) (tumors), Von Economo (1918) (encephalitis), and Richter and Trout (1940).

Finally Geretitzoff (1940) showed that the general cortical arousal reaction of vestibular nerve stimulation was still present following destruction of the cortex receiving vestibular afferents, and it was

Geretitzoff (1940) who first proposed that cortical activation occurred via sensory collaterals acting on the brain stem R.F.

Further evidence preceding the 1949 paper of Magoun and Moruzzi included the discovery by Magoun, Lindsey, and Bowden (1949) that basal diencephalic injury produced more profound EEG sleep changes than did the cerveau isolé preparation, in which optic and olfactory pathways could still provide afferents to the R.F.. Forbes (1949) found it difficult to assume that barbiturate anesthesia, which synchronizes the EEG, can be explained by a blockage of the classical sensory system; since in the anesthetized state, sensory impulses are readily conducted to the cortex. A diffuse cortical EEG effect was noted (Hess, 1929-30; Dempsy and Morrison, 1942) by stimulation of diencephalic and mid-line interlaminar thalamic areas. Murphy and Gelhorn (1945) found that hypothalamic stimulation increased the frequency and amplitude of low voltage electrocortical background activity. Jasper (1948) observed synchronization of the EEG accompanied by behavorial arousal, by stimulation of the posterior hypothalamus, massa intermedia of the thalamus, and the pariaqueductal area of the midbrain. Ward (1949) produced generalized increased voltage and frequency of the EEG following bulbar R.F. stimulation.

Monniere (1949) showed that generalized electrocortical desynchronization began after the evoked cortical responses from stimulation of a sensory system had ended and did not spread from the specific cortical region.

Original Paper

The foregoing experimental results are easily explained by the original paper, and aid in confirmation of, the conception of the R.F. Moruzzi and Magoun achieved through their experiments. As this fundamental paper is now a neurophysiology classic, the authors' important experimental findings will be discussed.

The experiments were performed on encéphale isolé (C1 cord transections) on anesthetized cats, with bipolar electrodes on the neocortical pial surface for recording the EEG and bipolar concentric electrodes implanted in the brain stem for pickup and stimulation. It was found that stimulation of the central brain stem throughout its length resulted in desynchronization of the EEF. This central channel of excitability in the brain stem included the ventromedial bulbar R.F., the pontile and mesencephalic tegmentum bordering the central gray and the caudal diencephalon in the dorsal hypothalamus and subthalamus. The desynchronizing effect of the EEG was unaffected by

atropinization and curarization of the animal. Stimulus frequencies of 50/sec. were necessary to produce the effect, with improvement in response to frequencies of 300/sec., and were independent of respiration, blood pressure, and heart rate. The effect of ventromedial bulbar stimulation on the EEG was found blocked by destruction of the mesencephalic tegmentum bordering the central gray but was unaffected if the midbrain was incompletely transected leaving only the former area intact.

On the basis of the above results it still would be tenable to hold that the ascending R.F., above described, activated the EEG by the antidromic excitation of corticifugal paths or by the dromic stimulation of known afferent paths. The former possibility is eliminated because: 1) sectioning of the basis pedunculi, containing the pyramidal tract and a cortico-bulbar-reticular path, did not inhibit the effect of bulbar stimulation producing EEG desynchronization; and 2) since bulbar stimulation resulting in EEG activation did not evoke antidrome potentials in the sensory-motor cortex or result in evidence of pyramidal tract stimulation, i.e., movement. R.F. stimulation does not act through the classical sensory paths (including the medial lemniscus lying adjacent to much of the ascending R.F.),

as 1) single shocks to the bulbar R.F. do not elicit sensory or motor cortical potentials as does lemniscal stimulation; 2) the excitable R.F. area was anatomically distinct from the lemniscal pathways; and 3) bilateral interruption of the lemnisci and spinal thalamic tracts did not alter the effect of medial-lateral bulbar R.F. stimulation on the EEG.

The fact that single shocks to the bulbar R.F. did not result in evoked potentials at higher levels along the activating system suggested to Magoun and Maruzzi that the R.A.S. must be composed of a series of reticular neurons with synapses which are iterative in nature.

The authors provided physiological evidence that, at least partially, the ascending R.F. exerts its cortical desynchronizing effect via the thalamus, probably the diffuse thalamic projection system.[2] 1) R.F. stimulation nearly abolishes the cortical recruiting response to low frequency stimulation of the diffuse thalamic (to cortex) projection system (and therefore influences this system). R.F. stimulation also abolishes contralateral thalamic electrical activity produced by stimulation of the thalamic projection system. 2) Chloralosane anesthesia synchronizes and reticular stimulation desynchronizes both the electrothalmogram and the EEG.

In summary Maruzzi and Magoun write, (17, p. 468),

"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. The effect is mediated generally on the cortex and is mediated in part, at least, by the diffuse thalamic projection system." (7, p. 472), "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 anesthesis or produce pathological somnolence."

Proof for a R.A.S.

At this point the experimental findings of the last few years which further supported the existance of a reticular activating system will be discussed.

Antonelli and Rudeger (1960) have shown that EEG arousal is not dependent upon the integrity of extralemniscal sensory paths ascending through the R.F. (4, p. 309). It will be recalled that Barris and Ranson (1936), and later Ranson and Magoun noted that with certain brain stem lesions, not involving the classic sensory tracts

(and in the cerveau isolé animal), sensory stimuli would not activate the EEG. Lindsay and Bowden and Magoun (1949), and Lindsay (1950) demonstrated that midbrain destruction involving only the R.F., produced continuous sleep or coma and such cats could not be aroused. Transection of the midbrain, sparing only the R.F., preserved the aroused state.

Numerous authors have mapped brain stem areas from which evoked potentials to several peripheral stimulus modalities may be recorded and have found them to lie in practically the same areas which when stimulated elicit EEG arousal. In other words the anatomical distribution of the R.A.S. overlaps the brain stem region showing convergence of evoked potentials (4, p. 323).

EEG arousal is not elicited by intercortical spread of afferent stimuli impulses, as both startling and often meaningful auditory stimuli have been shown to produce generalized EEG arousal after auditory cortex ablation (4, p. 326). Furthermore Jasper et al. (1950) have cut cortical slabs, leaving only white matter connections from below, without eliminating the EEG arousal response (4, p. 327).

In the Magoun and Moruzzi (1949) paper high frequency reticular stimulation was necessary to elicit arousal. In 1951 Magoun, Starzl and Taylor were able to evoke wide

spread cortical potentials by single shock stimuli to the R.F. (4, p. 311).

Segundo (1955) has well documented the simultaneous occurrence of behavioral signs of arousal and EEG desynchronization resulting from R.F. stimulation in anesthetized animals (4, p. 313).

Huttenlocker (1961) has provided further evidence for convergence of CNS afferents upon the reticular formation. He has shown a similar response to sound, touch, and light of some R.F. neurons; furthermore Katsuki (1961) has shown that for some R.F. neurons the acoustic threshold for R.F. firing was unchanged over a broad frequency range (12, p. 576).

Since 1949 the R.A.S. has been extensively mapped in the cat (Starzl, Taylor, and Magoun (1951)) and in the monkey (French, Von Amerongen, and Magoun (1953)) (4, p. 312). Besides the dog, cat, and monkey the existence of the R.A.S. has been confirmed in the pig, the rabbit, and the rat (4, p. 313), and the extent of influence and the role of the R.F. on the higher centers of the brain of all vertebrates appears to be similar (18, 19, 4).

The role of the R.A.S. in maintaining wakefulness appears to become more important as one proceeds up the phylogenetic scale in vertebrates. Strong afferent stimulation can briefly produce EEG arousal in rostral

R.A.S. ablated cats, but in the monkey a more profound depression of arousal develops; no induced arousal is possible; the animal appears comatose, and it frequently dies. Similar lesions in man produce a deep coma (4, pp. 329-330).

THE DEVELOPING CONCEPT OF THE R.A.S.

R.A.S. Afferents

Confirmed peripheral projections to the R.F. - R.A.S. which, when appropriately stimulated, have been shown to produce arousal are the following: Olfactory, visual, trigeminal, auditory, vagal, splanchnic, and virtually all varieties of peripheral somatic sensation via the spinal cord (4, p. 323). Afferents capable of producing synchronization (supposedly via the reticular synchronizing system to be described shortly) have been described by Pompeiano and Swett (1961). Low frequency stimulation to group II cutaneous sensory fibers, but not group II motor, or group III sensory-motor fibers produce synchronization (supporting Moruzzi's mechanism for Pavlovian sleep - to be discussed). High frequency high voltage stimulation of all these fibers produced arousal (20, p. 112). Zanchetti (1962) reviews the evidence showing the carotid and aortic sinus and aortic chemoreceptor

influence on the "reticular synchronizing system" (Gilhorn et al. (1952-53)), working with lightly anesthetized cats and monkeys, have graded the effectiveness of several types of peripheral stimulation in producing arousal. In order, the most effective arousal stimuli were found to be: Neoceceptive, proprioceptive, auditory, and lastly visual (4, p. 320). Rossi and Zirondoli (1956) have further established the supreme importance of somatic sensory afferents in producing arousal by showing that the trigeminal nerve was the most important cranial nerve in this respect (4, p. 333); however, its integrity is not essential for the waking state (4, p. 334).

Several central afferents to the R.A.S. have been described. Bremer and Tirzulo (1953) first showed that cortical stimulation could produce arousal (4, p. 321). The response has been produced in sleeping intact as well as drowsy encéphale isolé preparations. The effect is limited to certain cortical areas, especially the superior temporal gyrus, the tip of the temporal lobe, and the cingulate gyrus, as well as the sensory motor area. Rhinencephalic areas which on stimulation produce neocortical arousal include the limbic cortex, numerous anterior rhinencephalic regions, the amygdala, and the hippocampus-fornix (4, p. 322). Other sensitive

structures are the head of the caudate, fastigeal nuclei, and the anterior lobe of the cerebellar cortex. Evidence supports mediation of the above effects via the R.F. For example, descending volleys from areas of single cortical stimulation have been traced to the midbrain R.F. and the entorhinal area. Repetitive electrical and strychnine volleys were traced to the regions included in the R.A.S.. Furthermore, French, Hernandez-Peon, and Livingston (1955) show that cortical stimulation points eliciting arousal corresponded precisely with those cortical locations yielding reticular evoked potential (4, p. 325). They found the distribution of brain stem evoked potentials to correspond to the anatomical R.A.S. (midbrain R.F., subthalamus, dorsal hypothalamus, and several rostral thalamic nuclei including: N. ventralis anterior, N. reticularis, N. centrum medianum).

The Thalamic Reticular Formation

The thalamic reticular formation is the most rostral subcortical portion of the R.A.S. mediating both electrocortical synchronization and desynchronization of the neocortex. Large lesions in the anterior thalamic reticular system produce EEG and behavioral changes similar to those of R.A.S. destruction (21, p. 1318) except that the "sleep" is not as profound. Corticifugal and

cerebellofugal pathways impinge upon the thalamic reticular system as they do on more caudal R.A.S. structures. The non-specific thalamic system differs however in many ways from the more caudal portions of the R.A.S.. The most noticeable differences are that the more rostral components of the thalamic extension of the activating-deactivating system when stimulated evoke a more rapid and transient cortical desynchronization response as compared to the greater latency and enduring effects of more caudal R.A.S. stimulation. Furthermore, these more rostral components are compactly located and spacially differentiated, so that distinct areas of the diffuse projection system at this level "innervate" distinct cortical areas. Physiologic studies (21, p. 1311) have shown that the non-specific pathway through the thalamus begins in the interlaminer nuclei (especially portions of the N. centrum medianum) and in a few adjacent areas. At this point the activation pathway splits ventrally, transversing the mesioventral thalamus reaches the N. Ventralis medialis and N. ventralis anterior, and thence proceeds to the rostral pole of the N. reticularis, and finally to frontal and mesial cortical areas (21, p. 1312). The second path from the N. centrum medium extends (also by multicenaptic pathways) dorsally to the "limbs of the interlaminar system and the dorsolateral portion of the

N. ventralis anterior and reticularis" (21, p. 1312), and thence proceeds to posterior cortical areas. Rose and Jasper believe that the N. reticularis, which extends as a shell about the thalamus, may give origin to the final cells of the activating system. The final common path is poorly understood at present.[3] There is some evidence tentatively suggesting that the R.A.S. may also act on the cortex via a pathway through the internal capsule and caudate nucleus and possibly through other paths (21, p. 1313). Pupura (1963) disagrees with Jasper and presents some evidence which suggests that from the nucleus centrum medianum the R.A.S. discharge passes to specific thalamic nuclei inhibiting or potentiating the specific thalamic projection systems, and in this way providing a final path for R.A.S. action on the neocortex. (22)

Local Cortical Arousal

At this point it should be noted that elimination of certain specific sensory paths, or specific tracts, within the R.A.S. (cerebellar-rubral-cortical path for example) partially desynchronizes the EEG in local cortical areas. This is a discrete effect to be distinguished from the effect of reticular induced arousal. In the last few years, however, it has been shown that reticular cortical activation is not always homogeneous. Magoun, French and

Von Amerongen (1942) noted that with reticular stimulation cortical desynchronization was not completely uniform but was most marked in frontal, less so in parietal, and least in the occipital regions of the neocortex (4, p. 310). Many authors have recently shown that synchronization of the EEG by R.F. or peripheral stimulation may be altered by unilateral mesencephalic R.F. lesions or mesencephalic hemisection - such that the electrocortical synchronization occurs more readily and is more refractory to peripheral stimulation on the ipsilateral side of the lesion (23, 4). A similar and more pronounced asymmetry has been shown for posterior hypothalamic lesions. Thus there appears to be two incompletely separated EEG activation mechanisms for the two cortices in the R.A.S.. Hodes (1963) (22) has shown that unilateral lesions of the spinal cord at C1 also lead to a preponderant electrocortical synchronization of the ipsilateral hemisphere, and to a lesser extent such lesions produce a tendency to synchronization of the contralateral hemisphere. This result also suggests that structures concerned with EEG activation and perhaps arousal may extend caudally beyond the R.F. to the rostral spinal cord. The thalamic extension of the R.A.S., as will be described shortly, is possibly capable of even more specific cortical activation. Recent research has discovered the phenomenon of localized electrocortical

arousal. Examples of this are a change in the alpha rhythm of the occipital cortex to light stimulation, and local changes in rolandic rhythm to proprioceptive stimuli (/2, p. 575). Roitbak and Buthkusi (1961) stimulated the medial geniculate body and observed local activation of the auditory area. Karimoua (1961) (/2, p. 566) observed local cortical desynchronization to sound (desynchronization most marked in the temporal region) in animals under phenobarbital anesthesia. This desynchronization often was not accompanied by a change in R.F. potential rhythm or respiratory rhythm (changes which were concomitant in the absence of barbiturate anesthesia indicating that the R.A.S. may not be responsible for this local activation. Sokolov (/2) believes that local corti al arousal, which incidently appears to be essential to the orienting reflex, is mediated by extra-reticular activating systems. In support of a local cortical activating mechanism he sites the work of 1) Pupura and Housepian (1961) on surgically isolated newborn auditory cortex, direct stimulation of which evoked an 8-14 per second rhythm similar to thalamic interlaminar nuclei stimulation; and 2) KOGEN(1961) who apparently undercut visual and auditory cortical areas without loss of desynchronization to various peripheral stimuli. In this case isolation of the cortical area abolished the

desynchronization response. The above experiments appear to indicate the existence of local cortical activating mechanisms which may not be reticular in origin; furthermore they indicate that cortical activation mechanisms, quite possible the rostral portion of the R.A.S., may possible spread intracortically and be capable of intracortical stimulation.

The Hypothalamus and the R.A.S.

The importance of the intact hypothalamus in maintaining a waking state was suggested by Ingram, Barris, and Ranson (1936) and Ranson (1939). Moruzzi and Magoun (1939) described the posterior hypothalamus as one of the rostral components of the R.A.S.. The ascending hypothalamic outflow to the cortex through the non-specific thalamic projection system has been described earlier in the review. Ingram et al. (1951) (23) showed that extensive destruction of the hypothalamus, particularly the posterior hypothalamus, resulted in catalepsy with EEG and behavioral arousal being different. However these authors show that arousal was still possible with strong sensory stimulation. Hence it was shown that the intact posterior hypothalamus was not crucial in maintaining arousal. Furthermore, synchronization of the

EEG has been produced in a cerveau isolé (postcollicular transection) preparation by supression of the retinal dark discharge similarly indicating that activating structures remain intact above this R.A.S. level. (Bizzi and Spencer (1961) (20, p.309).

Further evidence decreasing the importance of the posterior hypothalamus as an essential component of the rostrol R.A.S. brings to light the poorly understood phenomenon of disassociation of electrocortical arousal from behavioral arousal. Under numerous experimental stimuli conditions this has been observed. Recently Feldman and Waller (24) have shown that the effects of posterior hypothalmic and midbrain R.F. lesions are not identical. They confirmed that in cats with bilateral posterior hypothalamic lesions the animals are unresponsive to stimuli and can not be aroused. However, midbrain R.F. stimulation in such animals resulted in EEG desynchronization with the cats showing no tendency to behavioral arousal to visual or auditory stimuli. These authors then placed bilateral lesions in the midbrain R.F. and found no change in the sleep-wakefulness cycle or in the arousability of these animals; however, the predominantly synchronous EEG pattern randomly desychronized without relation to behavior of the animal. Thus it appears that EEG desynchronization is not equatable with arousal;

and although behavioral arousal is to a large extent dependent upon the integrity of the posterior hypothalamus, EEG activation is not critically dependent on pathways funneling through this region.

A Reticular Desynchronizing System

Since the early work of Magoun and Maruzzi, until recently, the brain stem R.A.S.,extending from the bulbar to the caudal diencephalon, has been considered functionally homogenous. Abundant recent evidence has shown that there is a synchronizing, or sleep inducing area of the R.F. situated in the caudal pontine or bulbar R.F.(25,14) Bantini, Marruzi et al (1958-9) reported that pre-trigeminal mid-pontine transection of the cats brain stem resulted in a definite shift of the animals sleep-wakefulness cycle towards arousal. The duration of a desynchronized EEG was increased up to three to four times and was correlated with signs of behavorial arousal. Cordeau showed that hemisection of the brainstem at the mid-pons pre-trigeminal region similarly resulted in bilateral EEG and behaviorial evidence of arousal unaffected by encephale isole, vagotomized, and corotid sinus deenervated preparation. Only in the contralateral cortex did there appear desynchronization. The animals were awake and motionless with hyperreactivity to stimulation. This effect was produced

by hemisection down to the level of the rostral 1/3 of the bulb. Maruzzi, Magni et al (1959), in preparations with the basilar artery divided at the mid pons, noted that vertebral artery injection of a barbiturate resulted in desynchronization of the EEG, and carotid artery barbituate injection (effecting R.F. neurons rostral to the mid pons) produced ipsilateral synchronization. Cordeau showed that direct injection of local anesthetic or neuro toxic agents into the caudal pontine or rostral bulb produced EEG desynchronization. In the pre-trigeminal mid pontine preparation a prolonged borderline threshold arousal stimulus (nerve stimulation etc.) would activate the synchronized EEG. But eventually a desynchronized pattern would appear (Dell(1961)). If the pre-bulbar R.F. is sectioned the return of synchronization does not occur. (25,26) Cordeau has shown that acetyl-choline injected into the ascending R.F. produces behavorial and EEG sleep most readily if the caudal pons and rostral bulb is injected (the R.F. area supposedly initiating sleep and EEG synchronization). Similarly epinepherine and norepinepherine produce arousal and EEG desynchronization most readily if the R.F. rostral to the caudal pons is injected.

Magnes, Maruzzi, Pompeiano and Favale et al independently (1961) presented results which both support the possibility of R.F. inhibition and suggest a different

structural organization of this function.(25,20). These authors found that low frequency stimulation (five to twenty c.p.s.) of wide areas of the R.F. (and other apparently extrareticular structures) produced sleep and EEG synchronization in a partially desynchronized preparation that at low frequency stimulation, interspersed with foci the stimulation of which produced EEG and behavioral sleep, were foci which produced EEG and clinical arousal. (It will be recalled that Maruzzi and Magoun (1949) produced reticular activation only with stimulation frequencys greater than 50 per second). Both groups of authors concluded that low frequency stimulation of the brain stem selectively activates the synchronizing system. Cordeau (1960) proposes that the anatomical heterogenity of the R.A.S, suggested by the above experiments, is not the only explanation of these results. Possibly the efferents of a rostral bulb-caudal pontine reticular inhibitory system were stimulated to produce sleep and desynchronization.

Further evidence of a caudal R.F., synchronizing and sleep centered, is supplied by results of R.F. stimulation on cortical evoked responses. Peripheral arousing stimuli, or R.F. stimulation, will potentiate the effect of a cortical evoked response of a single shock stimulus to certain

sensory pathways. Cuerville, Walsh, and Cordeau have recently shown that the injections of pontocaine into the caudal (below midpons) R.F., or transection of the brain stem at the midpons (Armengal (1961)), results in increased amplitude of such cortically evoked potentials. As one would expect, pontocaine injection into the mesencephalic R.F. has produced diminished amplitude of cortical evoked potentials. As Cordeau suggests it appears that "under normal conditions the caudal brain stem R.F. exerts a tonic inhibitory influence on these (evoked) responses". (25, p.121) .

Bonvallet and Allyn (1963)(27) state that it is unclear if the "deactivating influences" described by Moruzzi's school for the midpontine pretrigeminal section specimen are due to "inhibition of the R. A. S." or "activation of synchronizing structure" (27,). These authors in contrast to Moruzzi, Cordeau, Zanchetti, et al. believe that the former explanation is correct. Their experiments show that: 1) tonic pupilo-constrictor activity of the Edinger Westfall nucleus is inhibited by specific R.F. discharge (Zybrozyna and Bonnvallet (1963)); 2) changes in parameters of cortical arousal (ease of attainment, duration, etc.) are found to correspond closely to R. F. "inhibition induced" changes in pupillary constriction. This indicates that the mechanism of the

change is the same, and hence suggests that cortical synchronization results from inhibition of the R.A.S.. Assuming this to be the case, the inhibitory area was next localized by these authors who note that in previous studies of R.F. inhibitory influence (spinal motor and autonomic inhibitary areas, etc., described by Alexander (1946), Magoun and Rhines (1947), Dell (1954), Wang and Brown (1956), and Block and Bonnvallelt (1961)) the ventral medial R.F. was the area implicated. Bonvallelt and Allen (1963), however, located a specific lateral area, a portion of the nucleus of the tractus solitarius at the level of the 10th dorsal motor nucleus, which when destroyed results in a definite tendency toward EEG desynchronization ("released reticular activation") as well as producing inhibition of several visceral functions. This inhibitory area probably acts at the mesencephalic level, as with mesencephalic transection certain effects due to ablation of the inhibitory area are abolished.

The character of R.A.S. inhibition produced by this area is specific. Ablation of the area does not alter the threshold or the duration of desynchronization during stimuli; but following stimulation the intensity, and often the duration, of the electricocortical arousal response are increased. Moreover, the R.A.S. appears unable to discriminate between the intensity and duration of

peripheral arousal stimuli; for where as the post stimulation activation response normally is related in duration and intensity to these stimulus parameters, after ablation of Bonnvallet's area it is no longer so related. That the maintenance of cortical arousal following stimulation does not depend upon corticofugal or supramesencephalic input to the R.A.S. is evident; for with mesencephalic transection superimposed upon ablation of the inhibitory area, the inhanced and prolonged arousal response remains. Bonnvallet and Allen show that the R.A.S. inhibitory area is anatomically and physiologically distinct from but adjacent to the vasodepresser points along the floor of the fourth ventrical. They show that ninth and tenth cranial nerve integrity adjuncts the inhibitory effect of the bulbar inhibitory neucleus described, but they point out that sectioning of these nerves does not eliminate the release from inhibition obtained by coagulation of the inhibitory neucleus. From the results of earlier work they conclude that the cephalic components of the ninth and tenth cranial nerve rootlets inhibits the R.A.S. whereas their caudal components are concerned primarily with R.F. vasomotor regulation. That the inhibitory neucleus does not mediate its effects by way of the low bulbar R.F. ventral medial inhibitory area is

shown by the fact that medial lesions at this level could not reproduce the inhibitory effect described above. Nevertheless the authors argue that the effects of their discrete lesion closely approximated and accounts for some of the inhibitory effects of mid-pontine pretrigeminal sectioning of the brain stem. For example, midpontine to rostral medulla transections, or possibly lower transections results in lasting electrocortical arousal, and destruction of the authors' bulbar area all prolongs post stimulation electrocortical arousal.

Bonnvallent explains his own previous conclusion that mesencephalic stimulation induced EEG arousal acts via the medial caudal medulla on the basis that medullary transection interrupted ascending impulses from, and procaine diffused to, the inhibitory bulbar nucleus. In support for their discreet medullary R.A.S. inhibitory center, the authors cite the results of Magnes (1961) that low frequency stimulation in the region of the tractus solitarius results in EEG synchronization, and the work of Bartoretti (1960) that carotid sinus distention inhibited, and bilateral vagatomy and Hering nerve section potentiated bursts of evoked and spontaneous sham rage.

The work of Bonnvallent thus further supports the

existence of a low pontine center important in the production of sleep and EEG desynchronization. The presence of such a center seems to be firmly established, and its mechanism may be as Bonnvallent suggests - inhibition of R.F. areas included in the R.A.S.

Hypothalamic Activating System

Kawamura et al have recently provided (1958-63) strong evidence for the presence of additional brain activating systems regulating other cortical areas. These appear to be located not in the R.F. but in the hypothalamus. The evidence suggests that EEG activation of the paleo- and archi-cortices is specifically the function of the anterior hypothalomus and posterior hypothalamus respectively, and an archicortex sleep pattern is a function of the anterior hypothalamic activity.

A discussion of the experimental results that have lead to this belief follows. (28, 29, 30) Arduini and Pompeiano (1955) noted that, paradoxically, hippocampal arousal waves may be present in the cerveau isolé animal. It will be recalled that in this preparation the neocortical EEG is synchronized and the animal appears to be asleep, presumably due to the lack of cortical tonus exerted by the transected mesencephalic R.F. (according to

Magoun and Langley's experiments). Arduini and Moruzzi (1953) induced the neocortical arousal pattern in the cerveau isolé cat by olfactory stimulation, but dissociation of electrical activity between the hippocampus neocortex was first produced by Green and Arduini(1954)(29) The work of Kawamura et al was done with cats and has been confirmed by Oshima et al in rats. Their results are included in the following statements. 1.) Cerveau isolé preparations show a neocortical sleep pattern and a paleo-archicortical continuous arousal pattern. 2) Massive destruction of the midthalamus similarly results in neocortical sleep with only slight decreased activity in the archi-paleocortices. The archi-paleocortices in contrast to the neocortex are easily activiated by peripheral or hypothalamic stimulation. 3) In cerveau isolé preparations hypothalamic stimulus threshold necessary to produce the EEG arousal pattern (a) in the neocortex is considerably elevated (although medial thalamic stimulation threshold to produce neocortical activation is unchanged) and (b) in the archi-paleocortices is unchanged. 4) Posterior hypothalamic lesions elicit deep sleep in both neocortical and limbic systems. (R.F. afferents to the neocortex pass through the posterior hypothalamus on the way to the thalamus and cortex). 5) In the cortical sleep patterns produced by posterior hypothalamic lesions,

the neocortex was easily activated by peripheral stimuli: whereas the archi-paleo cortical activation threshold was considerably elevated; and often the latter area could be aroused only by strong stimulation of the remaining posterior hypothalamus. 6) Preoptic lesions (anterior hypothalamus produced little change in the neocortical EEG, but remarkably lowered the archi-paleo cortical activity which was difficult to activate by peripheral, R.R., or midthalamic stimulation.

An interpretation of the above results follows. 1) Shows that the intact midbrain is necessary for neocortical activation but not for archi-paleocortical activation. 2) Suggests that although the majority of the reticular outflow to the neocortex passes through the medial thalamus (and hence destruction of this area results in neocortical sleep), the major pathway involved in archi-paleocortical activation does not pass through this area. 3) Suggests that EEG activation of the neocortex by impulses originating in, or in transit through, the posterior hypothalamus is dependent on the action of (or a pathway through) the midbrain R.F.; whereas activation of paleo-archi-cortices by posterior hypothalamic stimulation is not dependent upon the action of the R.F. 4) Suggests that activation of the old and new centers, at best, only partially depends upon passage

of impulses through the posterior hypothalamus, but 5) that neocortical arousal by R.F. stimulation is not crically dependent upon this pathway, whereas archi-paleocortical activation more nearly is dependent on this pathway. 6) Suggests that archi-paleocortical activation is also markedly dependent upon the integrity of the preoptic hypothalamic nucleus.

In a series of three papers in obscure journals these authors report the findings that: 1) Posterior hypothalamic stimulation activates the archicortical EEG, whereas 2) anterior hypothalamic stimulation produces a sleeping EEG pattern in the archi-cortex and an arousal EEG pattern in the paleo-cortex. 3) Posterior hypothalamic stimulation more easily activates the archi-cortex EEG than does R.F. stimulation, but R.F. stimulation more easily activates the neocortical EEG.

It is not easy for me to see why both ablation and stimulation of the anterior hypothalamus results in archicortical sleep; I would expect opposite effects; however, the evidence does appear to indicate that the hypothalamus rather than the midbrain R.F. is primarily concerned with archi-paleocortical synchronization and desynchronization.

Recent Poorly Understood Developments

Destruction of the brain stem R.F. was undertaken by Magoun and French (1952), Steller (1961), and Batsel (1961). The former authors observed a continuous synchronized pattern associated with inability to produce electrical or behavioral arousal and lack of awareness and voluntary motor activity. In preparations surviving longer than the above (3 months-2 weeks) Batsel observed that the cerveau isolé EEG after one month, returned to synchronization supposedly due to the intact rostral R.F. influence. Stellar's findings were similar with a medial midbrain tegmentl lesion resulting after one month in easy EEG and behavorial arousal.

Gleckman and Feldman (1961) (12,p. 564) have recently described extinction of arousal reaction to repeated reticular stimulation (in sleeping cats with chronically implanted electrodes). The excitability of the R.A.S. as a whole was unaltered as peripheral stimuli continued to evoke arousal. The reappearance of the specific arousal reaction occurred after about one half hour.

"The Human Diffusely Projecting System" (31)

Recently a few animal results relating to R.A.S. and mediation of cortical evoked potentials have been confirmed in the human. Skull recording electrodes

monitored effects of various modalites of peripheral stimulation on the E.E.G. in a comatose patient with Jakob Creutzfeld's disease. In this patient electrocortical background activity was reduced to a minimum due to extensive cortical and cerebellar destruction (supposedly eliminating the tonus exerted by these structures on the R.A.S.). Cortical evoked potentials with bilateral symmetry were recorded following peripheral stimulation. That this discharge was mediated by the R.A.S. is evidenced by the fact that 1) response latency was greater than that of conduction along classical sensory paths, 2) the nature of the response was widespread, 3) different modalites of stimuli produced similar cortical discharge, and 4) barbiturate narcosis abolished the response. The authors were successful in demonstrating occlusion[5] of evoked potentials by temporally approximating different modalitys of stimulation.

Footnotes: THE RETICULAR ACTIVATING SYSTEM

(1) p.5 The following historical discussion is based in part upon that of Maruzzi and Magoun in The Brain Stem Reticular Formation and Activation of the EEG, EEG Clinical Neurophysiology, 1, 455-473, 1949.

(2) p.10 The thalamic recruiting response is the 1-1 cortical potential response to low frequency stimulation of the diffuse thalamic projection system. In this response the corticsl potential rapidly recruits to a maximum amplitude and then slowly varies in amplitude.

(3) p.18 See Scheibel in the anatomical part of this review

(4) p.29 His previous conclusion was based on results that medullary transection or procaine injection into the ventral medial midbrain R.F. blocked EEG arousal.

(5) p.35 Occlusion is the inhibition of one evoked potential by the presence of another evoked potential and has a basis in convergence of neurons on the R.F.

AUTONOMIC MECHANISMS AND VISCERAL CONTROL

THE "MICRO-MILIEU INTÉRIEUR"

Dell (1960) (11) has emphasized that epinepherine, CO_2, and O_2 blood levels significantly influence the R.A.S. and ascending-descending reticular motor-sensory effects. He further has provided substantial evidence that these structures act directly on the reticular formation. For example, his evidence in favor of "adrenergic mechanisms" in the R.F. is discussed. Dell cites the following in support of a direct R.F. effect of I.V. epinepherine. 1) Reticular effects are produced when variables such as CO_2 and B.P. remain constant. 2) Mesencephalic R.F. ablation supresses the arousal response to epinepherine, and brain stem section rostral to the mammilary bodies, does not affect epinepherine potentiation of spinal motor tone, whereas this effect is abolished by midpontine brain stem transection. 3) Extractable epinepherine and norepinepherine are concentrated in subcortical regions of the CNS.overlapping the reticular formation. 4) Compounds reinforcing epinepherine effects (cocaine, etc.) excite reticular activity as do adrenergic agents in general. Furthermore, some compounds with antiadrenergic effects (ergotamine) block reticular activity.

One may speculate that the CO_2 effect Dell observed was mediated via the recently identified medullary hydrogen ion chemoreceptor. However, mesencephalic transection and not suprabulbar brain stem transection abolishes this effect.

Dell (1960) believes the adrenergic R.F. mechanism supported above is as important a reticular mechanism underlying tonic reticular activity as is peripheral and CNS R.F. input. He furthermore implicates reticular adrenergic sensibility in maintenance of intra-reticular activity thereby maintaining arousal, and in phasic and tonic activation of cortical arousal and motor activity due to circulating epinepherine (which in fact is probably released by fight - flight reactions in response to reticular stimulation produced by hunger, hypoxia, threatening environmental stimuli, or other variations in the milieu exterior or interior). Dell visualizes visceral-somatic integraters modigying the milieu intérieur on the basis of changes within its own "micro-milieu intérieur".

French writes (32) that Eular, Sodarburg, and Dell have shown an augmented blood CO_2 directly produces generalized augmented R.F. neuronal firing whereas O_2 inhibits neuronal activity, via the carotid body (in contrast to Dell's supposition). EEG arousal can be produced by injection into the systemic circulation of acetylcholine

and anticholenstrases as well as cholinergic drugs in general (31, p. 1289). This forms a basis for Rothballer's (1956) hypothesis of brain stem cholinergic mechanisms, similar to brain stem adrenergic mechanisms of Dell and Rothballer. French (1960) also concludes that these substances act via the reticular formation. In support of this he notes that specific decortication abolishes the response to colinergic as well as adrenergic agents, and systemically these drugs produce reticular evoked potential changes similar to those produced by peripheral stimulation. Dell has shown that the mesencephalic R.F. is indispensable in adrenalin induced neocortical arousal. Adrenalin appears to produce archi - paleocortical arousal by action on the posterior hypothalamus[6]. The autonomic mediators may play an important neuro-conduction role in the brain stem mechanism of the R.A.S., for Ingvar has obtained electrocortical desynchronization in the surgically isolated cortex (1, p. 1289).

Recently conflicting results have emerged concerning brain stem adrenergic and cholinergic mechanisms. The suggestion of a cholinergic mechanism in the R.A.S. on the basis of atropine blockage of the R.A.S. is contradictory to Loeb, Magni and Rossi's results that atropine has no effect on arousal to single reticular or peripheral stimuli (20, p. 309). Evidence for adrenergic mechanisms is not

supported by the lack of epinepherin EEG arousal effect with intracarotid rather than I.V. epinepherine ((Capon (1960) and Montigazzini et al. (1959)). The lack of EEG desynchronization with subliminal dosage I.V. epinepherine superimposed upon sub-threshold R.F. electrical stimulation (Bradley (1960)) (2o, p. 309) certainly does not support an adrenergic mechanism. Brain catacholamine levels, furthermore, have not been related to animal behavior (Vogt (1960)).

Some recent evidence in favor of adrenergic reticular mechanisms has appeared. It has been suggested that vasopressin is the vasopresser released with R.F. stimulation, and epinepherine may act in this way. Dell (1960) notes that pyrogallal, a metabolic epinepherine potentiator, prolongs arousal to I.V. epinepherine. Several authors have apparently disassociated the pressor and cortical effects of adrenaline, and Montigazzini and Glasser (1960) have injected D.O.P.A., intracarotid or I.V., with EEG activation not accompanied by a systemic presser effect. An important objection to the above results is that the up-take of D.O.P.A. is much greater than that of norepinepherine, and as Zanchetti (2o, p. 310) emphasizes, micro pipette application of norepherine and acetylcholine to R.F. neurons does not influence their extracellularly recorded discharge (Curtis and Koizuma (1960)).

In conclusion, the concepts of adrenergic and cholinergic reticular mechanisms, although far from clear, are probably valid descriptions of reticular physiology.

RETICULAR VISCERAL CONTROL

A generalized autonomic function of the brain stem was suggested in 1916 by the work of Mullar and Sherington. Exploring the floor of the fourth ventricle they electrically stimulated swallowing with concurrent tachycardia and arrest of respiration. It is known today that the medullary R.F. also contains afferent and efferent mechanisms centrally controlling the sneezing, swallowing, salivary, sucking, and vomiting (R.F. emetic center) reflexes. R.F. centers control bladder activity, modify rectal tone, and assume control of the hyperglycemic reflex to peripheral nerve stimulation. (32, p.1959-62) Hemingway et al have indicated that temperature control neuronal pathways from the preoptic hypothalamic nuclei enter the spinal cord via the brain stem tegmentum, and inhibition of shivering can be produced by stimulating this R.F. path. (1, p.1299) Furthermore, the respiratory and vasomotor centers are located in the reticular formation, and the R.F. has important influences on the hypothalamic-pituitary-adrenal axis.

The cortical and peripheral stimuli modification of autonomic reflexes is well known. This influence, in many instances, has been shown to be produced by action through the R.F. French notes, for example, that all cortical areas projecting to the R.F. have been implicated in the control

of G.I. function and that, in one experiment, cortical stimulation producing arousal and arresting motion, with a stronger stimulus, facilitated movement, produced tachypnoea and roughening of the fur. (1, p1249)

Reticular control of respiration, the cardiovascular system, micturition, the G.S.R., as well as R.F. influence on the hypothalamic-pituitary-adrenal axis will now be discussed in more detail.

Reticular Control of the Micturition Reflex

The effect of R.F. stimulation on micturition was noted as long ago as 1888. Cortical modulation was first reported in 1847. Through transection experiments, Tang and Rush (1955-6) described several brain regions modifying the sacral micturition reflex: 1) a cerebral inhibitory region. 2) a posterior hypothalamic inhibitory region, 3) a mesencephalic inhibitory area, 4) an anterior pontine facilitory area. (32, p.961).

Until recently experimental results have been difficult to reproduce because intravessicle pressure was not adjusted before recording stimulation points modifying intravessicle pressure. (33) A number of stimulation, ablation, and transection experiments by Kuru et al (33) have recently localized a medullary vessico constrictor center to the ventral lateral R.F. and a bulbar vessico-relaxer

center in the dorsal medial R.F..The mesencephalic constrictor center is located in the R.F. bordering the lateral central grey and adjacent structures including the superior colliculus. It is connected with the bulbar constrictor center by the tectobulbar and the lateral reticulospinal tracts. The midbrain relaxer center is located in the dorsolateral tegmental R.F. and intercollicular and inferior collicular regions, and it is connected to the corresponding bulbar area by the techtobulbar tract. Bulbar as well as sacral centers are undoubtedly involved in reflex control of the bladder, as well as serving as centrifugal paths; for infrabulbar transection, but not suprabulbar transection, abolishes vesical contraction from stimulation of the central stump of the cut pelvic nerve.

The Galvonic Skin Reflex

Wang et al (1956) have described reticular facilitory and inhibitory areas for the galvonic skin reflex. (32,p.961). The hypothalamic and reticular structures above the intercollicular level facilitate, and the R.F. below this level inhibits, the G.S.R.,as indicated by transection experiments. Cl cord transection abolishes the facilitory and inhibitory effects of lesions at var-

ious levels. Medullary cooling or anesthetization, in confirmation of transection experiments, produces facilitation of the G.S.R..

Toshikatsu et al (1963) (34) has studied the G.S.R. of cats in response to R.F. stimulation. He showed that microelectrode stimulation of the bulbar ventral medial R.F. produced decreased amplitude of skin potentials and a decreased amplitude of the G.S.R. potentials, confirming Wang and Brown (1956). Stimulation of the lateral bulbar R.F. produced an increased skin potential and an increase of the G.S.R. potential. The R.F. effects varied directly in magnitude with strength, frequency, and duration of R.F. stimulation. There appeared to be a rebound of skin potential. This was related to intensity and duration of the inhibition. Stimulation of some R.F. areas produced inhibition or facilitation of the G.S.R. according to the frequency of stimulation.

Thus it appears that the control of autonomic reflexes elicited by the R.F., and specifically the G.S.R., may be dependent upon the site of R.F. action and upon several perameters of stimulus character.

The Respiratory Center

The respiratory center is located in the caudal half of the medullary R.F. Pitts, Magoun and Ranson, (1939)

located the respiratory center by noting stimulation points eliciting only maximal inspirations and expirations. They located the respiratory center immediately dorsal to the inspiratory center and adjacent to the subventricular grey matter. Several cytoarchitectronic cell groups are included in these centers, but the nucleus giganto celularus forms a large part of the inspiratory center and appears to be the site of origin of reticulo spinal fibers for both the inspiratory and expiratory centers (4). Because certain cytoarchitectronic areas included as points of maximal stimulation do not have reticulospinal fibers, Rossi and Zanchetti suggest that these may represent areas concerned with inhibition of respiratory movements, etc. They point out that since maximum inspiratory movements are not elicited by pontine (pneumotactic center) stimulation, although here R.F. efferents are numerous, this later center probably acts only on the medullary centers.

Vasella (1961) (35) has precisely located the "noeud Vital" of the medullary respiratory center in the rabbit. Bilateral destruction of a 1x1 m.m.area extending rostrally from the rostrol extent of the ventral reticular nucleus into the caudal nucleus gigantocellularis resulted in cessation of respiration.

That the carotid body effect upon respiration is

mediated through the brain stem respiratory center has been known for many years. Leusen (1950) first described a cerebral spinal fluid perfused H^+ chemoreceptor for modification of respiration (36). Several authors have considered the medullary R.F. to be the site of this chemoreceptor which may be as important as the coretid body in homeostasis of respiration. Mitchell et al (1963) has apparently localized this receptor to the ventralateral surface of the medulla (36).

The respiratory center is not autonomous; Redgate (1963) presents evidence that the caudal hypothalmus exerts a tonic facilatory influence upon the inspiratory center and an inhibitory influence on the brain stem expiratory center. His results indicate that although respiration is maintained by depression or ablation of the hypothalamic center, a 23% decrease in minute volume ensues. The Hering Breuer reflex as well as bicarbonate and other effects on the brain stem respiratory center are significantly modified by hypothalamic ablation (37).

Todeuki Sumi (1963) has shown that reticular respiratory neurons do not act directly on phrenic or intercostal motor neurons but through a series of internucial neurons, which also are interposed in the afferent path from the respiratory muscles (38). He has provided examples of significant modifications of respiratory motor-

neuron activity associated with reflex phenomena ordinarily not thought to involve respiration. This suggests that sub-respiratory center modification of respiration may be significant.

Recently a very interesting correlation has emerged between the physiology and the location of the respiratory center and descending reticular inhibitory and facilitory systems (of Magoun). Hoff and Breckenridge (1954) have considered the inspiratory and expiratory centers to be respectively portions of the descending facilitory (rostral) and inhibitory (caudal) reticular centers. Activity of a portion of the facilitory system (inspiration) would be in their opinion, inhibited by higher centers exerting their effect on the bulbar inhibitory center. In support of this hypothesis (4, p299-302) 1) mid pontine transection and vagotomy results in inspiratory spasm (apneusis) and concomitant extensor rigidity. 2)Subsequent medullary transection results in loss of decerebrate rigidity and rhythmic breathing (loss of inhibitory center tonus). It is interesting that the first procedure results in hypertension and tachycardia, and the second procedure abolishes this effect. Rossi and Zanchetti (4, p.301-3) summarize objections to the theory and conclude that it is valid in part only; 1)the inspiratory center partially overlaps the reticular muscle

tone inhibitory area. 2)Stimulation maping of R.F. areas concerned with respiration, vasomotor, and motor facilitation result in no correlation of magnitude or duration of effects. 3)Post-corricular decortication and vagotomy produced apneustic breathing without decerebrate rigidity, and rigidity and apnuesis may be disassociated easily by other means.

Nevertheless it appears that the brain stem respiratory center is closely linked to ascending and decending reticular systems. Hoff (1963) (39) notes that the tachypneic phase of Cheyne Stokes respiration is usually accompanied by blood pressure and pupil diameter changes, heightened awareness, and increased postural reflex activity.

Functional correlation of reticular arousal -sleep mechanisms and respiratory mechanisms are presented in the work of Bulow (40) (1963) who showed that P_aCO_2, and ventilation vary in striking correspondence with EEG patterns signifying stages of sleep-arousal. With certain drugs it is possible to dissociate EEG and respiration changes. Non-respiratory reticular areas appear to tonically modify the respiratory center response to P_aCO_2, with a degree of modification varying with the degree of wakefulness. A strong desynchronizing influence, for example, has been shown to prevent apnea due to hypocapnea (40).

Fink (1963) (41) Hugelin and Cohen (1963) (42) provide further demonstration of general R.F. function in brain stem respiratory control. Working with curarized, vagotomized preparations these workers found that stimulation throughout the reticular activating system rostrol to the respiratory center produced concomitant EEG desynchronization, reflex changes, tachypnaea, and hyperpnaea. The magnitude and character of the stimulation response was highly constant throughout the R.A.S., and the response could be duplicated by peripheral nerve or natural arousing stimulation.

Although there is a difference of opinion on the basic functional organization of brain stem respiratory neurons, the complex organization of pneumotaxic, apneustic, inspiratory, and expiratory centers held in recent years appears, to this observer, to be giving way in weight of experimental evidence to a more simplified description of respiratory organization. The major points of disagreement center on the origin of rythmicity of respiration. The three major views are: 1) that the activity of the inspiratory -expiratory center neuronal aggregate is spontaneous, 2)that external sources of stimulation are requisite for inspiratory-expiratory center rhythmicity, and 3)that the inspiratory center is continuously active and requires inhibition from without the inspiratory-expiratory center complex for respiratory rhythmicity (43).

The idea that pontine, apneustic, and pneumotactic centers are necessary to explain respiratory rhythmicity arises in results of apneustic respiration (breath holding plus short expiration) occuring in vagotomized animals with pontine lesions, and in results of respiratory response to selected pontine stimulations (44, p.573). However, it has been shown that rhythmic respiration remains if the pons is completely separated from the medulla (Hoff and Breckenridge, 1949) (44, p. 579) and on the basis of the latter author's data equating ascending and descending reticular activity to respiratory center activity, it is most reasonable to conclude as does Salmoiraghi (1963), that pontine "respiratory neurons may be simply non-specific facilitory reticular elements or else inspiratory or expiratory neurons called into play under conditions of moderate to intense respiratory activity" (44, p.579).

Several important facts are provided by the recent microelectrode studies of Salmoiraghi on the spontaneous and evoked discharge of single nerve cells in the region of the brain stem respiratory centers. The results indicate that recruitment and inhibition of neurons showing respiratory periodicity occurs respectively under conditions of increased and decreased respiratory stimulation. Secondly, neurons of inspiratory or expir-

atory periodicity are more difficult to depolarize as the rate of impulse conduction increases. Thirdly, progressive deafferentation of brain stem slab, consisting of the hemisected medulla and pons, with the contralateral hemi-brain stem as a control, results in progressive silencing of neurons showing respiratory periodicity. Brief single stimulation of the cut end of the slab temporarily results in renewed periodic firing of single neurons. Salmoiragahi notes that neurons with respiratory periodicity have been located in the pons, (Wang, and Cohen) and in the rostrol lateral medullary R.F. and lateral to and about the obex. An important observation of such neurons is that they fire in marked synchrony during either inspiration or expiration, depending upon the neuron. Salmoiraghi states, "available evidence indicates that synchrony results from interconnections between members of the same population" (44, p 578)

Salmoiraghi puts forward an impressive explanation of respiratory center action on a basis of the above experimental data. In essence, feedback between neurons of coupled inspiratory neuronal aggregates initiates and maintains inspiration after external tonus (from non-specific facilitory - inhibitory R.F. and other sources) excites a few neurons in the aggregate. As neurons discharge frequency increases so does its resistance to polarization; hence the activity of the inspiratory neurons

diminishes, and this in turn releases the inhibition of the inspiratory neuron grouping upon the expiratory neuron aggregate, some members of which, those having the most tonic R.F. facilitation, begin to discharge, activating the whole expiratory aggregate, until resistance to de-polarization develops releasing sensitive inspiratory neurons from inhibition - and the cycle repeats.

Reticular Regulation of Hypothalamo-Pituitary Function

Fortier (45, p. 230) describes several lines of experimentation which have indicated reticular formation control of the anterior hypophysis, for which a nerve pathway (the dorsal longitudinal fasiculus of Schultz) has been recently described. Okinaka et al. (1960) and Endroczi et al. (1960) have noted increased A.C.T.H. activity with midbrain R.F. stimulation. Slusher et al. (1961), with ventral midbrain tegmental stimulation in encéphale isolé cats, evoked a specific and rapid decrease in adrenal effuent corticoids. Midbrain transection prevents A.C.T.H. response to some stressful stimuli (Guiliani (1960)), (Davis (1961)). Slusher (1960) found that rostral pons lesions in the rat 1) dorsally, resulted in increased corticosteroid release with stress and 2) ventrally, inhibited their release with stress.

Clinically midbrain lesions have been reported which are associated with hyperphagia and inhibition of ovulation (45, p. 809), and other results have led to the hypothesis of reticular formation control upon the secretions of T.S.H. and gonadotropans (45, p. 476). There is some evidence that the R.F. may act on the hindbrain as well as the hypothalamus to release hypothalamic neurohumors (47, p. 230).

As an example of research in this field one paper (46) will be discussed. Tsubokawa and Sulin have recorded electrohypothalamogram potentials in 272 areas of the ventromedial hypothalamus.[7] It was shown that 45 percent of these areas fired spontaneously and 11 percent could be fired by amygdaloid or septal stimulation. Stimulation of the lateral mesencephalic R.F. increased both the amplitude and the firing rate if the hypothalamic response was initiated by septal stimulation. If the medial mesencephalic R.F. was stimulated the effect of septal stimulation was now facilitated and that of amygdaloid stimulation was inhibited.

The results of this experiment, as well as supporting an R.F. influence on the important hypothalamic areas, appears to show that the reticular control may be spatially differentiated within the R.F. and may, at least in this experiment, act via rhinencephalic structures.

There is abundant evidence for R.F. influence on the posterior hypothalamus. Sharpless and Rothballer (1961) (48)[8] have shown that electrical stimulation of the R.F., pariaquaductal gray, and tegmentum brings about a release of neurohypophyseal hormones. In discussing this, Kleiman and Gutler (1963)(47, p. 401) state "(this) can only be explained by impulses transmitted from the reticular formation area of the medulla to the supra-optic and para-

ventricular nuclei of the hypothalamus". Sharpless and Rothballer suggest this influence to be responsible for the reflex antidiuretic effects of pain and excitement. Gilbert (1956-61) has shown that the midbrain ablation leads to water intake disturbance in rats (49, p. 475). Chang (1937) stimulated the central end of the cut vagus nerve, in spinal cord transected animals, and observed an increase in blood pressure; and Tayler et al. (1951) observed this response in the recipiant in a cross circulation experiment (48, p. 914).

Much experimental research (especially Henry (1956)) has shown that A.D.H. is released as a result of carotid sinus and right atria-pulmonary artery stretch (volume) receptors. These receptors tonically mediate their influence by the vagus and glossopharyngeal nerves to the lower brain stem and thence, in some manner, to the hypothalamus. The R. F. has been strongly indicated in this function (49, 474-475). A.D.H. output is also controlled by osmoreceptors in the hypothalamus and possible in areas of the medulla.

The control of aldosterone secretion via carotid and atrial stretch (volume) receptors also appears to be medicated via the reticular formation to an unknown diencephalic structure which secretes adrenoglomerulotropin. This hormone in turn stimulates aldosterone secretion, (49, p. 477-481). Bilateral rostral midbrain lesions

adjacent to the cerebral aqueduct (near Sharpless and Rothballer's lesions which influence A.D.H. activity) markedly reduced aldosterone secretion (Newman and Taylor (1958-62)), and other midbrain R. F. lesions resulted in increased aldosterone secretion. Favele and Taylor conclude (in their 1963 review of the literature on vascular regulation) (49, p. 484) with the suggestion that in the brain stem R.F. is "the driving force which maintains a state of tonic non-discriminatory stimulation of vasomotor activity, A.D.H. secretion, and aldosterone output", and "against this background of tonic stimulation, the vascular reflexes in turn exert inhibition".

Brain Stem Vasomotor Control

Dittmar (1870) first localized CNS control of the cardiovascular system to the rostral bulb. Ranson and Billingsby next localized vaso pressure and depressure areas to the floor of the fourth ventricle; and through the work of Monniere, Lang and Ranson, Alexander, and Bach, it was discovered that vasomotor changes attributed to stimulating the floor of the fourth ventricle could be obtained by stimulating the underlying bulbar pontine R.F. and many adjacent non-reticular structures. Chen (1937) noted that brain stem pressor responses were accompanied by generalized sympathetic effects (producing practically all sympathetic

responses) thus indicating that brain stem vasomotor regulation might be but a small part of a general sympathetic control.

Peiss (1960) postulated that the brain stem vasomotor control area was but a way station to more rostral control areas, expecially the hypothalamus. Wang and Chai (1962) however show that brain stem transection to a level within the pons leaves intact cardiovascular reflex mechanisms to reticular, peripheral nerve, and carotid sinus stimulation (30). Chai and Wang, furthermore, have repeated the experiments of Peiss but were unable to find the depressed cardiovascular responses to medullary and peripheral stimulation, in animals with mid-collicular transection, as reported by Peiss. Their micro electrode stimulation studies confirm localization of brain stem centers eliciting blood pressure and heart rate responses to the dorsal bulbar R.F. extending to the floor of the 4th ventricle. The onset of effects appeared instantaneously with hypertensive responses usually accompanied by tachicardia and a positive inotropic effect. Hypotension conversely accompanied bradycardia. Although points yielding maximum cardiopressor responses were localized to a cross-sectional area of two by two millimeters, stimulation of a large portion of the R.F. could elicit minor H.R. and B.P. changes; and the apparent area of the vasomotor centers could be increased by increasing stimulus voltage. In general vasopressor-cardio-

accelerator points were well grouped in the dorsal R.F., with the depressor-deaccelerator points lying ventral to them and being somewhat scattered. Pressor-depressor responses were bilaterally symetrical, but inotropic effects occurred especially with left bulbar stimulation and cardio-acceleration with right bulbar stimulation. The later finding, earlier described by Cotton (1953), and Randall (1957), suggests unilateral brain stem representation of some structures involved in the sympathetic cardiovascular modulation. Brodal (1957) has noted that areas giving rise to maximum vasopression as described by Wang, Alexander and others do not contain reticulo-spinal neurons (4, p. 265), suggesting that the vasopressor center acts via the vaso-depressor area. However, although a dramatic fall in arterial pressure accompanies C1 cord transection (4, p. 266), reticular stimulation in such a preparation results in increased blood pressure suggesting a humoral mechanism (possibly vasopressin according to Sharpless and Rothballer (1961), but not supported by the short latency response found by Chai and Wang (1962)).

In an extensive study on the vasomotor response to stimulation of 192 cecerebrate and 62 anesthetized cats, Kovalev and Bondareo (1963) have carefully mapped the brain stem with microelectrode stimulation to precisely localize vasopressor centers (51). In their results they do not

distinguish between degrees of vasopressive effect, and hence the results are not strictly comparable to those of Wang (1962). Their important findings are summarized: 1) Brain stem pressor sites outnumber depressor stimulation sites 3-1; 2) Brain stem stimulation sites producing increased blood pressure are not well localized but are found throughout large areas of the bulbar-pontine brain stem; 3) There is no separation of stimulation points producing decreased blood pressure from those increasing blood pressure - rather they are intermingled; 4) Stimulation of points eliciting pressor or depressor effects does not elicit the opposite effect (reversal of sign) when stimulus duration, frequency, or voltage is altered (many reticular responses are frequency dependent); 5) Transection of the brain stem rostral to the pons does not affect the sign but diminishes the amplitude of stimulation effects (confirming the autonomicity of the brain stem centers).

The exact location of presser-depresser areas, in Kovalev's experiments, although localized to the pons and medulla, does not correspond closely to the results of earlier investigators. However, the results of these authors and Wang (1963) are of more significance than earlier experimentation, as much smaller electrodes were used than those of previous stimulation studies. On serial reconstruction of bulbar pontine cross sections the authors have correlated areas of successful stimulation to location of brain stem nuclei, tracts, etc. and find some correlation.

Important areas producing responses were the tegmental reticular nucleus, inferior ventral reticular nucleus, middle vestibular nucleus of Schwalke, vestibulo-spinal tract, medial reticulospinal tract, tegmental olivo tract and tecto-spinal tract.

It thus appears that the vasopresser centers are not well spacially seggregated or divisible in to presser-depressor areas, at least to the resolving power of present day experimental technique. It may be naive to consider Wang's spacially seggregated areas of maximum and minimal vasomotor response to represent physiologically distinct systems of neurons. More likely, the organization underlying the specificity of brain stem vasomotor control is diffuse, in the same sense that Vasella's "noeud vital" of respiration is likely to be just the localization of a crucial pathway in the respiratory control mechanism.

Kovalev (51) notes that specific bulbar pontine R.F. stimulation, by Soviet workers, has recently been shown to produce changes in the lumen of cerebral vessels as well as concomitantly opposite effects on the diameter of intestinal and peripheral vasculature. This suggests that reticular vasomotor centers may selectively control wide spread vascular response. Although reticular cardiovascular CONTROL is important, hypothalamic and probably other C.N.S. structures alter the centers res-

ponse. Alexander (1963) (52,213-17) reviews the evidence for cardiovascular reflex mechanisms probably not under control of the brain stem homeostatic sympatheto constrictor system. The cholinergic hypothalamic centered, temperature control system for the head and chest is an example.

Footnotes:

AUTONOMIC MECHANISMS AND VISCERAL CONTROL

(6)P.39 The effects of blood pressure and cerebral vascular dilitation were controlled in this study.

(7)P.55 The results were obtained in 23 cats with rostral pontine lesions to insure interruption of the descending autonomic pathways, as they might be activated by R.F. stimulation.

(8)P.55 In this experiment fluctuations of blood pressure and movements of the de-enervated nictitating membrane were ascribed to the release of vasopressin released in response to R.F. stimulation (after the effect of other possible mediators had been ruled out).

CONCLUSION

In the past two decades considerable investigation has been focused on the Reticular Formation as the probable area of basic integrative interaction, or as suggested by Livingston, "the area of Integrative transaction". The work of Magoun and Moruzzi (1949) relating the R.F. to wakefulness is generally considered the foundation to the current investigative emphasis. Numerous fields of investigation are currently engaged in R.F. research.

It is known that the Reticular Formation both modifies sensory and motor phenomena and regulates the level and focus of consciousness. It plays a basic part in visceral control. We can look forward to the fruit of further research in this field.

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