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Present knowledge of the structure, function and pathology of the brain provides a better understanding of the events which lead to postoperative failures in the intracranial surgery of acoustic tumors. Part one of Dr. Bebin's presentation appeared in Volume 16, No. 1 — the Spring issue. In this second part, special reference is made to vascular and respiratory changes and to disturbances of consciousness.—Ed.

The Cerebellopontile Angle, The Blood Supply of the Brain Stem and the Reticular Formation — Part II

Anatomical and Functional Correlations Relevant to Surgery of Acoustic Tumors*

Jose Bebin, M.D., Ph.D.**

At the time when little was known about the structure and functions of the brain stem, Flourens (1842) considered the medulla oblongata as "*le noeud vital*". Modern neurophysiology has proved the correctness of this expression. No other part of the CNS intervenes in so many and such vital functions as the reticular formation of the brain stem. In fact, nowadays when the question of the functional role of the brain stem is raised, we first think of its role in the process of consciousness and related functions. We should, however, be aware of the limitation of this restriction, not only because lesions in the brain stem in man will rarely — if ever — be restricted to the RF. The study of the structure and fiber connections of the brain and interconnections of its various parts makes clear the artificiality of considering the RF as a separate part of the brain stem.

Respirations, vasomotor responses, regulation of sleep-wake up rhythm, consciousness, are but a few of the activities under the realm of the RF.

III. THE ANATOMY, PHYSIOLOGY AND PATHOLOGY OF THE BRAIN STEM RETICULAR FORMATION (BSRF)

The name RF designates an area of the tegmentum of the brain stem composed of multipolar cells of various sizes included in masses of fibers, interwoven in all directions, and presenting a reticular appearance.

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Bebin

This structure was regarded as unspecific in nature. In it the MLF are embedded, as well as the fibers system and cranial nerve nuclei. The RF was regarded as an association system which was mainly concerned with regulation of the local activities of the brain stem.

The old anatomists had already observed that long ascending and descending fibers arose within the RF, and physiologists had found that localized areas of these structures, e.g., the respiratory and vasomotor centers, influenced the activity of neurones in the spinal cord. Modern physiological investigation has enlarged the role of the BSRF to include much broader activities.

Anatomically, the RF has indistinct boundaries and extends within the brain stem from the lower medulla to the diencephalon, incorporating both small and large multipolar neurones. Short and large axons provide rich interconnections within the formation, allowing both slow and rapid conduction. Individual cells extend their processes over a large area, creating optional anatomical conditions for stimulation, by collaterals coming from many different specific fiber pathways, and from adjacent nuclear masses.

In functional terms, the RF has a much greater extension in both rostral and caudal directions than purely structural definition would imply.

Structurally, the RF of the brain stem may be defined as those tegmental cells which are not cranial nerve nuclei, sensory or cerebellar relay nuclei, olivary or pontine nuclei. Many attempts have been made to segregate the cells of the BSRF into definite "nuclei", but the nature of the brain stem organization makes this an exceedingly difficult task, and few authors are in agreement on the boundaries of these "nuclei". Olszewski and Baxter (1954) produced the first complete cytoarchitectonic map of the RF in man. The main nuclear groups which these authors distinguished can be identified in other mammals (Fig. 22).

1. The *lateral reticular nucleus* lies below and to the side of the inferior olive. Three subnuclei, not clearly delineated, can be distinguished: *pravicellularis*, *magnocellularis*, and *subtrigeminalis*.

2. The *nucleus reticularis tegmenti pontis* lies immediately dorsal to the pontine nuclei and consists of large multipolar nerve cells.

3. The *paramedian reticular nucleus*, a small group of cells, covers the inferior olive near the median plane.

4. The *nucleus reticularis gigantocellularis* extends from the rostral half of the inferior olive to a plane of the facial nucleus occupying the medium two-thirds of the entire reticular formation. It is composed of large, medium and small nerve cells.

5. The *nucleus reticularis pontis caudalis* lies rostral to the previous one which is poorly demarcated. It consists of large multipolar neurones.

The Blood Supply of the Brain Stem

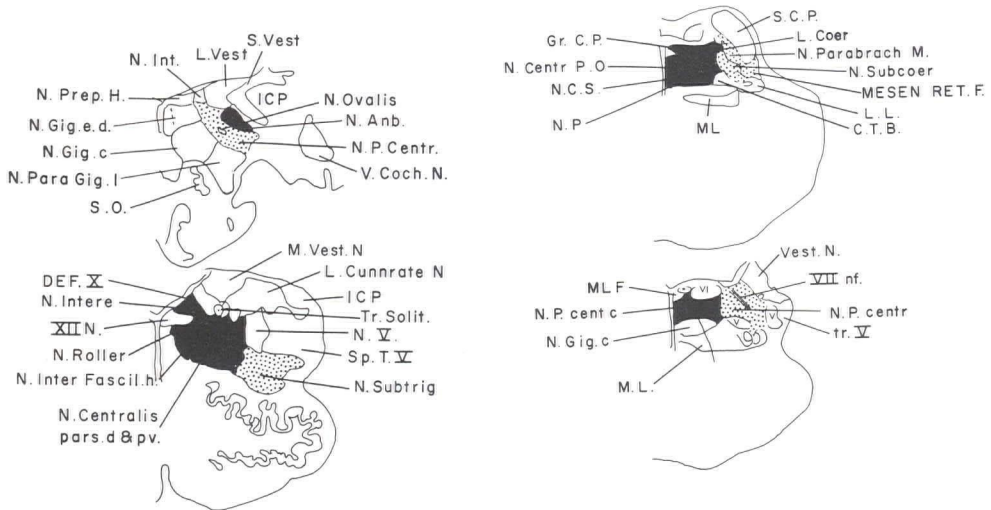


Figure 22

The brain stem reticular formation of man (Redrawn from Olszewski and Baxter, 1954)

6. The *nucleus reticularis pontis oralis* continues rostrally to the nucleus reticularis pontis caudalis without precise limits and extends into the midbrain reticular area.

7. The *nucleus reticularis parvicellularis* is a small formation lying dorsolaterally to the nucleus reticularis ventralis and nucleus reticularis gigantocellularis.

8. The *nucleus reticularis ventralis* is a caudal continuation of nucleus reticularis parvicellularis.

9. The *nucleus reticularis lateralis* is situated between the nucleus reticularis ventralis and the ventrolateral surface of the medulla.

A practical approach is to divide the RF into medial and lateral portions. The *medial RF* includes all the reticular cells, including the spinal cord and intralaminar thalamic nuclei, and the more centrally placed (medial two-thirds) reticular cells of the brain stem. The *lateral RF*, on the other hand, is only encountered in the lower brain stem, and roughly includes the reticular structures in which the descending and principal sensory nuclei of the trigeminal nerve are embedded.

The cytoarchitectonic differences of various nuclei of the RF furnish strong evidence that they cannot be functionally equivalent. There are also differences between their ascending and descending connections. Most of the cells of the lateral RF send their axons to the adjacent medial RF. None of them give off large ascending or descending axons. The cells of the medial RF send their axons either rostrally or caudally and some have axons which bifurcate into ascending and descending branches.

Bebin

The *ascending reticular system* is part of and not the whole RF. It contains the arousal system, but it is not known whether or not the arousal system coexists with the ascending RF.

The majority of the long ascending fibers arise from two fairly well circumscribed regions of the medial RF (Brodal and Rossi, 1955). One is in the medulla and includes the caudal part of the nucleus reticularis gigantocellularis; the other is in the pons and comprises the caudal part of the nucleus reticularis pontis caudalis (Fig. 23). Experimental studies (Nauta and Kuypers, 1958) have shown that the destination of these ascending fibers is the so-called unspecific thalamic nuclei. Other fibers do not pass the mesencephalic RF. Fibers arising from this area appear to reach the hypothalamic, preoptic area and the medial septal nucleus.

Sensory impulses were originally assumed to enter the RF from collaterals of the specific sensory pathways. However, it has been shown by Rossi and Brodal (1957) that the path for impulses entering the RF from the spinal cord, largely if not

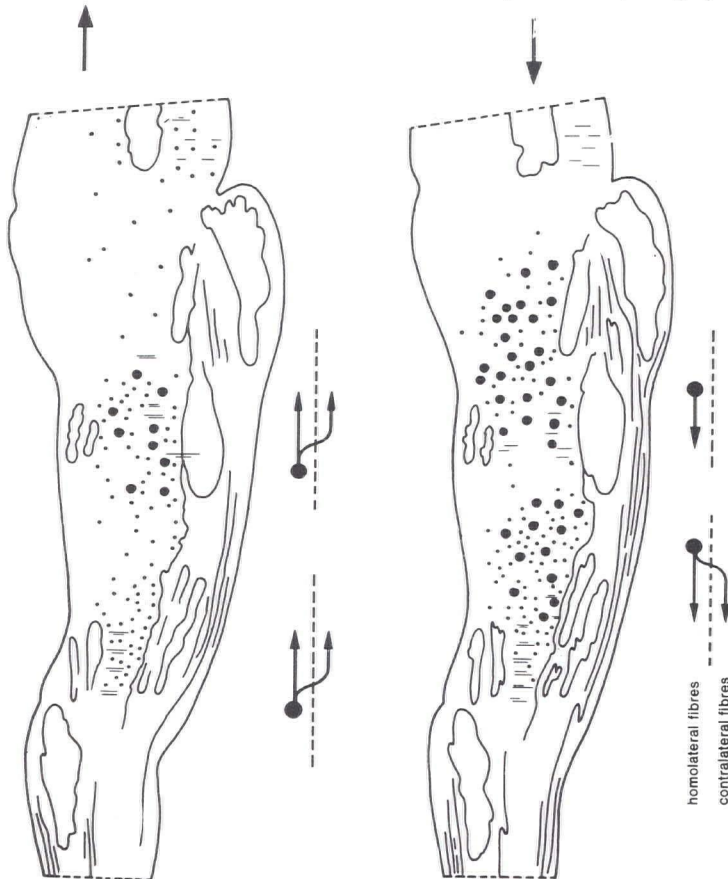


Figure 23

Origin of the ascending and descending fibers of the brain stem reticular formation. The intensity of the projection is indicated by the spacing of the dots. (From Brodal 1957.)

The Blood Supply of the Brain Stem

exclusively, is by direct spinoreticular fibers. The fibers terminate in the medial RF (caudal part of the nucleus reticularis gigantocellularis and adjoining regions in the medulla and in the caudal part of the nucleus pontis caudalis) in the regions which give origin to long ascending axons.

A large number of impulses from sensory cranial nerves and their nuclei reach the RF. Whether this is established alone or predominantly by collaterals of the secondary sensory ascending fibers requires further study. There is, however, evidence of some primary afferent fibers to the RF in the XI-th, X-th and V-th nerves ending in the RF close to the solitary tract (Torvick, 1956) and lateral vestibular nuclei.

The influence of cortical stimulation on the activity of RF is well known and the afferent fibers in the forebrain arise chiefly from the sensory motor cortex. Kuypers (1956) found that the premotor cortex projects in cats to the medial reticular formation of the medulla, while Rossi and Brodal (1956) also found in cats cortical projection in both pontine and medullary reticular formation. These end in the most caudal regions of the RF which give origin to reticulospinal fibers.

The descending reticular system

Clinical and experimental studies in animals have demonstrated that the RF is capable of influencing spinal motor and autonomic mechanisms. These effects are mediated chiefly by direct reticulospinal fibers. Several regions of the medial RF have been known to give rise to long descending axons (Kohnstamm, 1899). Torvick and Brodal (1957) found they originated from two main regions of the RF: one in the *medulla* (nucleus reticularis gigantocellularis, and rostral part of nucleus reticularis ventralis and medial part of nucleus reticularis pontis caudalis) and another in the *pons*, (nucleus reticularis pontis oralis and the rostral part of nucleus reticularis pontis caudalis). These regions are situated more rostrally, although partly overlapping with the ones giving off ascending fibers.

The reticulospinal fibers arising from the pons are ipsilateral and those arising in the medulla are bilateral, though chiefly ipsilateral. The reticulospinal fibers terminate at caudal levels of the spinal cord (Nyberg-Hansen, 1965). As already mentioned, the lateral RF of the medulla and pons projects medially and so influences descending reticular neurones in the medial RF.

Afferent fibers to the descending RF are from two main sources: the forebrain and the cerebellum. Mention should be made of tectoreticular fibers. The reticular afferent from the forebrain has already been mentioned and arises mainly from the cortex and basal ganglia (Kuypers, 1955). The cerebellar afferents to the RF arise chiefly from the fastigial nuclei, although some contribution comes from the dentate nuclei. The cerebelloreticular fibers reach the brain stem RF through the inferior cerebellar peduncle travelling ipsilaterally as fastigioreticular fibers, or contralaterally as the uncinate fasciculus.

Bebin

In summary, the RF may be divided into: (a) *descending reticular system*, situated chiefly in the midline of the pons and rostral medulla which receives cortical and cerebellar connections and projects to the spinal cord; (b) an *ascending reticular system* situated in the caudal part of the pons and medulla, which receives fibers from the spinal cord and projects to the thalamus and midbrain nuclei, and (c) a third system situated chiefly in rostral part of the midbrain which has both afferent and efferent connections with the hypothalamus, basal ganglia and septal areas.

It is well known from clinical and experimental data that the RF is capable of influencing spinal motor and autonomic mechanisms. These effects are mediated chiefly by direct reticulospinal fibers arising from two main regions of the BSRF in the pons and in the medulla. These regions partly overlap with those giving off long ascending axons. Since the large ascending and descending axons give off collaterals during their course, the rostral and caudal regions of RF have opportunity for influencing each other. This morphological arrangement is in agreement with clinical and functional studies in man and animals. A very close relationship exists between influences of the RF on consciousness and on the activity of the spinal cord. How closely these functions may be linked is shown by the existence of reticular cells with axons which dichotomize shortly beyond the origin in a long ascending and long descending branch.

Emphasis has been placed on the anatomical features of the RF showing it to be composed of a number of "units". It would be an oversimplification to consider them as mutually independent. Histological studies with the Golgi method (Scheibel and Scheibel) demonstrate that there is an anatomical basis for a rich interplay between various "units" (Brodal, 1965). Likewise, it would be an oversimplification to regard the RF as a structure only remotely related to other parts of the brain. The anatomical data invalidates this view. Reticular axons end in all sensory nuclei and motor cranial nerve nuclei and also in neighboring regions.

The structural similarities between certain structures in the brain stem and the RF, and between their interconnections, raise the question if the function attributed to the RF may be not peculiar to it. In addition, the RF has important connections with many other parts of the brain (hypothalamus, basal ganglia, cortex) that must be considered when studying a complex function like consciousness. Clinical experience has demonstrated that disturbance of consciousness may follow damage to many other parts of the brain other than the RF.

In human pathology, a lesion of the brain stem will almost never be restricted to the RF. It is not surprising that the symptomatology in such cases is complex and may affect several functions. The close topographic relationship of the RF to pathways and nuclei should particularly be remembered in explaining the symptomatology and pathophysiology of the lesions.

It is suggested, on a structural basis, that each cell group of the RF might have its own functional significance. Unfortunately, the reticular neurons and their con-

The Blood Supply of the Brain Stem

nections are not clearly segregated in the anatomical sense. Much intermingling occurs. There is little expectation, therefore, that electrophysiological exploration of any region of the RF may give pure effects, without contamination by simultaneous stimulation of other reticular neurones and axons. Hence, electrical stimulation of the RF gives little more than an inventory of influences exerted by the RF on other parts of the CNS and, in this way, some understanding of its significance. This approach has shown that an astonishing variety of effects can be obtained from this comparatively small part of the brain. Rossi and Zanchetti (1957) list the following responses:

- (1) Respiratory responses.
- (2) Vasomotor and other autonomic responses.
- (3) Effects on postural tonus and on phasic movements.
- (4) Effects on the electrical cortical activity.
- (5) Effects on the electrical activity of subcortical centers.
- (6) Effects on sensory neurones.
- (7) Electrical responses of the cerebellum.

Before we discuss these, it should be remembered that in human pathology a lesion of the brain stem will never be restricted to the RF. Because the RF is surrounded by fiber tracts or nuclei related to more or less specific functions, it is not surprising that the symptoms of involvement of the brain stem are multiple and may affect several functions. The close topographical relationship of the RF to motor and sensory pathways and nuclei should be remembered in the interpretation of the effects of such lesions. In discussing the enigmatic function called consciousness, due account should be given to the many parts of the brain, besides the RF.

Discussing the problems on the surgery of acoustic tumors, Hitselberg and House (1966) considered that some of the difficulties at surgery were related to vascular and respiratory disturbances secondary to interruption of the vascular supply of the corresponding centers in the brain stem.

They observed that out of 114 patients operated on for acoustic tumors 34 had vital signs changes during surgery. The most frequent was a rise in blood pressure with variable pulse alterations, irregularities, increase or decrease of pulse rate. The respiratory alterations were inconstant and consisted of apnea of variable duration. In many instances these changes heralded more serious complications determining a modification of the initial operative procedure. In only 12, the planned total excision of the tumor was completed.

Toward the end of the procedure for surgical removal of a right acoustic tumor, a 50-year-old man had a sudden rise of blood pressure from 110/65 to 170/80 and an increase of pulse rate from 60 to 85 mm associated with respiratory arrest for five minutes. The vital signs did not return to normal during the rest of the operation. The patient did not regain consciousness postoperatively and expired two days later. The postmortem examination revealed edema, necrosis and infarction of cerebellum and middle cerebellar peduncle and upper third of the pons on the right. The blood vessels showed no occlusion. The authors suggest that the pathological changes present (ischemia, necrosis and edema) could be attributed to prolonged

Bebin

arterial spasms without occlusion. It is widely held that when a main artery is impaired, all its tributaries and collaterals go into spasm of variable duration.

During the operation of acoustic tumors, the retraction of the cerebellar cortex is often sufficient to produce an infarct of a part of the cerebellar cortex and a certain number of arterial anastomoses will be occluded in this manner.

Respiratory and vasomotor responses are usually considered to result from excitation of highly specialized portions of the reticular formation. Typical respiratory patterns and vasomotor responses are obtained from relatively circumscribed portions of the RF and neurones showing rhythmicity are limited in number. Anatomically, however, the location of respiratory and vasomotor centers cannot be clearly distinguished from neurones which are responsible for other reticular effects. The pathways carrying respiratory effects and vasomotor influences to the spinal centers have not been dissociated from those which mediate the regulation of tone and reflexes.

Respiratory Responses

There is general agreement that the so-called respiratory center is located in the RF at the level of the caudal half of the medulla oblongata (Pitts et al, 1939). Opinion is not unanimous, however, as to the extent and topographic organization of the structures responsible for inspiration and expiration.

Two centers, *inspiratory* and *expiratory*, are described for control of respiration. Not all experimental results are in agreement. For example, Brookhardt (1940) was unable to separate on stimulation two separate zones for inspiration and expiration in the dog. Recent studies are in favor of a random distribution of inspiratory and expiratory neurones working under reciprocal inhibition. The arrangement suggested by Pitts has found the greatest acceptance. The expiratory center lies in the dorsal RF, just beneath the subventricular grey matter, dorsal to, and cupping over the cephalic end of the more ventrally placed inspiratory center. If this arrangement is compared with the cytoarchitectonic organization of the RF, it will be seen that points given maximal inspiratory responses are found within the nucleus reticularis gigantocellularis (except its most rostral and dorsal part), the rostral part of the ventral reticular nucleus and a portion of the lateral reticular nucleus (Fig. 24). Expiratory responses are evoked chiefly by stimulation of the nucleus reticularis parvicellularis and the dorsal part of the nucleus reticularis gigantocellularis.

Inspiration and expiration exhibited an autonomic rhythm which can be stopped neither by elimination of all afferent stimuli, nor peripherical paralysis of spontaneous respiratory movements, nor interruption of the connections between the respiratory center and higher centers. Pitts (1940) considered that the expiratory center produced expiratory movements by inhibition of the inspiratory center. Spontaneous electrical activity recorded with electrodes in the inspiratory and expiratory center is synchronous with the phases of the respiratory rhythm. The activity of the inspiratory neurones stimulates the expiratory neurones which, in turn, inhibit the first.

In the intact organism, the medullary respiratory center is under a regulatory mechanism through superimposed pontile, diencephalic, and occasionally cortical

The Blood Supply of the Brain Stem

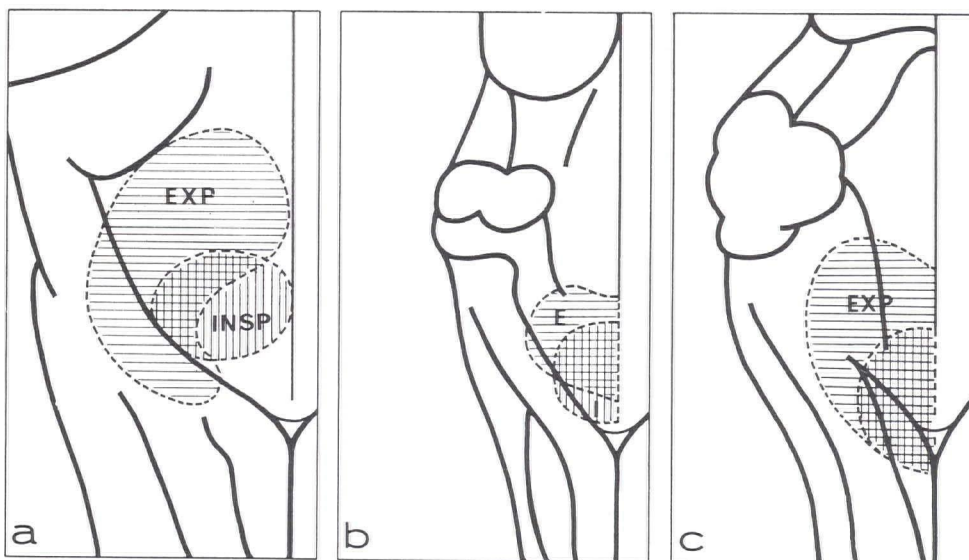


Figure 24

Regions of the lower brain stem affecting respiration when stimulated. a) macaque, b) cat and c) sheep. (From Oberholzer and Tofani, 1960)*

“respiratory centers”. But the bulbar respiratory center represents, according to present knowledge, the minimal substrate with which a regulated respiratory activity can be maintained and under appropriate conditions can react to CO_2 stimulation or the peripheral influences.

Transections of the brain stem between the collicular plate and the striae acoustica lead (in rabbit, cat and dog) to respiratory changes which vary according to the level of the section. After decerebration by intercollicular transection, spontaneous respiration is lightly changed. Sections of the brain stem, behind the inferior colliculus, also fail to produce respiratory changes, provided the rostral portions of the pons remain intact. Spontaneous respiration is only slightly changed when the section is made to remove the rostral third of the pons. When in addition the X-th nerve is cut, long periods of respiratory arrest occur with maximal respiratory depth, *apneustic respiration*. One continues to observe this apneustic respiration even when the most caudal segment of the pons remains intact. A transection below the striae acoustica, separating the pons from the medulla, ends the apneustic respiration. The medullary animal shows either eupneic respiration or very deep breaths in regular succession: *gasping respiration*.

These ablation experiments have led to the assumption that there are two pontine respiratory centers. In the rostral part of the tegmentum of the pons lies the inhibitory respiratory activity, the *pneumotaxic center*. A more extensive region in the middle

*Oberholzer, R.J.H. and Tofani, W.O.: The neural control of respiration. In Handbook of Physiology, Section I: Neurophysiology, Vol. 2, pp. 111-29. Washington: American Physiological Society, 1960.

Bebin

and caudal pontine tegmentum is called the *apneustic center*. This center exerts a strong tonic effect in the medullary inspiratory center. When the pneumotaxic center is destroyed, apneustic respiration appears. From experimental data, the locus coeruleus may represent the pneumotaxic center. Its isolated bilateral destruction results in apneusis in the vagotomized cat. In man its destruction produces severe dyspnea with gasping or periodic (Cheyne-Stokes) respiration. The apneustic center has not yet been precisely located. It probably includes medial and caudal areas of the pontine reticular formation.

Plum and Posner (1966) have observed occasionally *periodic breathing* that may superficially resemble Cheyne-Stokes respiration in expanding lesions of posterior fossa.

The *hypoventilating periodic breathing* of the low brain stem injury often changes into cluster breathing, which is a sign of ponto-medullary dysfunction.

Central neurogenic hyperventilation (sustained rapid hyperpnea) occurs in patients with dysfunction of the brain stem tegmentum, usually destructive lesions (produced by infarcts, anoxia, transtentorial infarction and hemorrhage), between the lower midbrain and lower third of the pons, destroying the RF ventral to the aqueduct and fourth ventricle.

Apneustic breathing usually occurs in pontine infarcts (basilar artery occlusion).

Ataxic breathing (Biot respiration) results from lesions of the medullary respiratory center. It represents a disruption of the reciprocal interrelations between inspiratory and expiratory neurone populations. Many pathological processes in the posterior fossa can impair the respiratory rhythm. It is typical of medullary compression that respiration fails before circulation.

Rapidly expanding lesions (cerebellar or pontine hemorrhage) may produce *respiratory arrest*. Slow expanding lesions affect respiration less often, unless they directly compress or destroy the central portion of the caudal medulla.

Cortical lesions, and metabolic disturbances affecting the brain stem RF and higher centers, suppress modulating impulses to the respiratory center. These may result in respiratory dysrhythmia, such as periodic breathing or other such hypernea which leads to hypocapnea.

Vasomotor Responses

In the last part of the Nineteenth Century, the integrity of the medullary structures was considered essential for the maintenance of normal cardiovascular tone. Early in this century, Bayliss (1901) introduced the dualistic vasomotor center theory according to which, a vasoconstrictor and a vasodilator center, acting reciprocally governed the activity of the vascular tone. In the second and third decade, a number of investigators (Ranson and Billingsley, 1916) chartered by neurophysiological stimulation of the medulla, more or less limited regions at the base of the fourth

The Blood Supply of the Brain Stem

ventricle that produce vasoconstriction and vasodilation. Experimental evidence available today suggests that the medullary control of vasomotor tone is affected only via variation in the vasoconstrictor discharge. More recent authors speak of medullary pressor and depressor regions that affect the vasoconstrictor tone and, hence, the arterial blood pressure by excitation and inhibition, respectively, of the spinal vasoconstrictor neurones.

Stereotaxic experimental stimulation of the medulla oblongata has shown that *the pressor region* comprises an extensive zone within the lateral RF with its principal extent in the rostral two-thirds of the medulla and also from structure outside the RF (i.e., vestibular nuclei). A *depressor region* is localized in the medial reticular formation and extends chiefly into the caudal third of the bulb (Alexander) which includes the larger part of nucleus reticularis gigantocellularis and rostral part of nucleus reticularis ventralis (Fig. 25). The importance of the medullary pressor area for tonic cardiovascular discharge was demonstrated by Alexander (1946). In decerebrate cats, he recorded a continuous discharge in the inferior cardiac nerves and in the cervical sympathetic. Transection of the medulla just rostral to the obex, (a procedure which cuts most of the pressor area from its descending connections, but leaves the depressor area more or less intact), produces an equivocal reduction in arterial pressure and cardioacceleratory tonic

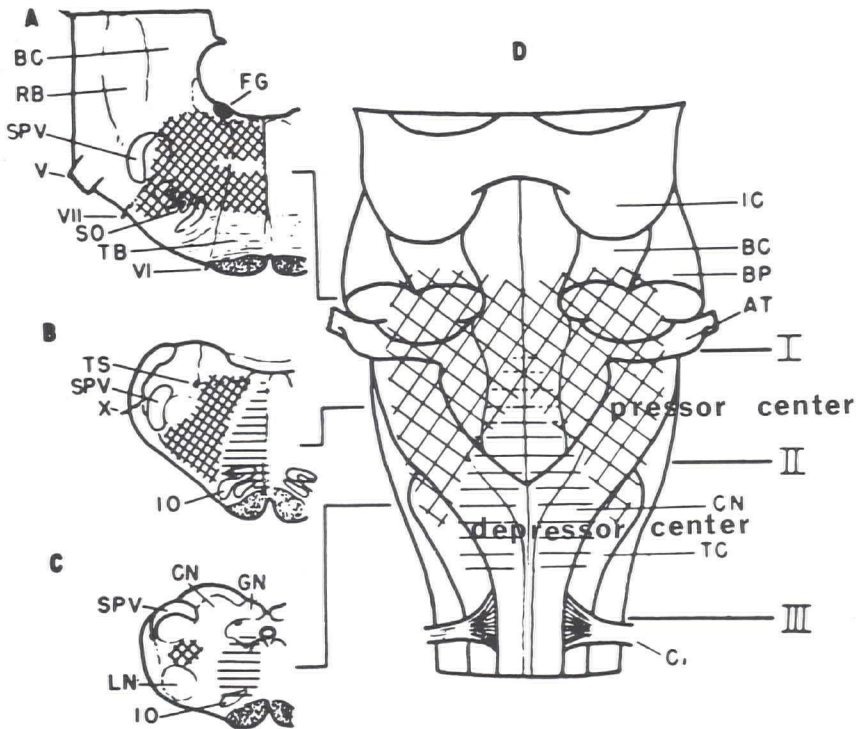


Figure 25

Localization of pressor and depressor centers in the brain stem of the cat. (From Alexander.) Pressor regions indicated by cross hatching; depressor regions by horizontal ruling.

Bebin

discharge in the inferior cardiac nerves. Alexander further showed that the depressor area probably is tonically active, exhibiting a continuous inhibitory action in spinal cardiovascular neurones. Transection at C-1 level results in an increase of tonic discharge in the inferior cardiac nerves indicating a release from a tonic inhibitory influence. The vasoconstrictor (pressor) neurones do not send their axons directly to the preganglionic sympathetic neurones of the spinal cord. Their impulses are conducted caudally by polysynaptic pathways. The impulses from the vasomotor centers followed the lateral tract to the lateral horn of the spinal cord and reach the end organ via the sympathetic nerves.

According to Alexander's observations, we have a steady stream of exciting impulses from the pressure area to the spinal vasoconstrictor neurones. The ultimate discharge of the latter would be the result of the balance between the excitatory and inhibitory medullary discharges to the preganglionic vasoconstrictor neurones of the cord.

Medullary Cardiac Centers

In principle, the medullary control of cardiac activity is organized like the vasomotor control, although with the difference that cardiac control possesses an efferent parasympathetic inhibitory pathway, *the vagus nerve*.

The heart rate has been considered to be controlled by the tonic and reciprocal actions of two medullary centers, one acceleratory and the other inhibitory, but the exact localization is unknown. The inhibitory center is thought to be in connection with the vagal nucleus. The acceleratory impulses run in the sympathetic outflow and the inhibitory impulses in vagal fibers.

The Medullary Spinal Vasomotor Pathways

The excitatory fibers of the pressor regions pass to the spinal vasomotor neurones in the ventrolateral column (Wang and Ranson, 1939). Hemisection of the cord reduces but does not abolish pressor responses resulting from ipsilateral medullary stimulation. Partial crossing of the excitatory fibers seems to occur at spine level. The inhibitory fibers from the depressor region pass in the dorsolateral column (Alexander). These fibers cross extensively in the medulla.

The integrity of the medullary vasomotor area is essential for the pressor and depressor reflexes elicited by specific receptor in the carotid sinus and in the aortic arch, and also from similar reflexes elicited by stimulating various efferent nerves (Alexander). Thus, there is a feedback mechanism between the central and peripheral organs.

Disturbances of Consciousness

According to accumulated experimental and clinical data, the brain stem plays a fundamental role in the maintenance of consciousness. However, the significance of the brain stem neural mechanism underlying consciousness does not imply at all that it is the only structure of the brain responsible for this function. Complex cerebral functions, such as consciousness, are the result of the integration of activities

The Blood Supply of the Brain Stem.

of several structures. Each one of them must be related, however, to some neural system of specific importance. The brain stem, and in particular its reticular core, would be the important critical area for the normal regulation of level of consciousness.

We do not intend to discuss the philosophical and psychological definitions of consciousness nor its controversial terminology and classifications. Briefly, it should be recalled that consciousness has two components, one being its crude on-off quality and the other its content.

Psychological and clinical pathological studies in man have demonstrated that the content of consciousness depends on the cerebral hemispheres (Chapman and Wolff, 1959). Physiological studies in animals have concentrated more on the crude quality of consciousness and on attempts to relate it to states of wakefulness and sleep, as well as to the pathological state of coma. These investigations have focused mainly on structures within the brain stem. In this region an important unspecific activating mechanism, *the ascending reticular activating system*, was discovered by Moruzzi and Magoun (1949) within the rostral reticular formation, extending from the midbrain to hypothalamus and thalamus with a diffuse projection to the cerebral cortex. This system profoundly influenced the arousal and the EEG. When stimulated directly it produced desynchronization and behavioral arousal. When it was destroyed, a slow synchronized EEG and coma followed. Neither of these could be reversed by strong sensory stimulation of the intact sensory pathways. The view became prevalent that consciousness was due to the specific arousal effects of the ascending reticular activating system (ARAS) stimulating the cerebral hemispheres. Similarly, it was assumed that sleep and coma were due to passive failure of a physiologically or pathologically inactivated ARAS.

As pointed out previously, the RF has indistinct boundaries and a diffuse polysynaptic structural organization without precise specific units. Consequently, the ARAS is more a physiological than anatomical entity.

In animals, behavioral and EEG patterns of coma are produced by all transections of the diencephalon, midbrain and rostral part of the pons (Batini, Moruzzi, et al, 1959). Transections through the caudal pons or medulla do not produce such effect. The rostroponitile transection is regarded as the most caudal one capable of producing coma. Based on these facts, the theory that the neurones of the rostral pontine RF, and to some extent of the midbrain and diencephalon, exert an arousing or activating influence on higher centers and are thus responsible for the maintenance of consciousness. The RF of the lower pons and medulla appear to have important influences in certain stages of sleep and in the EEG, but do not seem to be required for the maintenance of animal consciousness.

In recent years experiments in animals (cats) have shown that some brain stem lesions are followed by a reduction of the time spent in sleep and even an almost suppression of sleep (Jouvet, 1962; Rossi, et al, 1963). Moreover, injections of barbiturates into the vertebrobasilar system of animals (cats, rabbits) produce arousal

Bebin

from sleep (Rossi, 1964) revealing the existence in the brain stem of neurones having a "deactivating" or sleep inducing function (Jouvet, Rossi, Moruzzi). The most important group of these neurones is located at midpontine and medullary levels in the region of the nucleus tractus solitarius. The precise anatomical identification of the deactivating neurones is lacking and some of them belong to the RF. (Rossi, 1965).

In summary, experimental neurophysiology indicates that almost the entire brain stem is involved in the mechanisms responsible for changes of consciousness with important regional differences. The level of consciousness may be either increased (activation or arousal) or decreased (deactivation or sleep) by brain stem mechanisms. The "activating" structures within the RF are rostral to the "deactivating" ones, but both are closely interrelated and a mutual inhibitory influence is likely to exist between them. Both seem to be influenced by other cerebral structures, such as the cerebral cortex, and from sensory receptors. (Rossi, 1964).

Activating mechanisms, with functional properties basically similar to these revealed by experimental neurophysiology, have been described for man but the problem of the topographic distribution of the activating neurones is still open to discussion.

The studies in man, of necessity, are based on clinical and pathological observations. It has been the experience of most clinicians that focal or purely unilateral lesions of the cerebral hemispheres do not produce unconsciousness. However, this view is not unanimous and two purely unilateral cerebral conditions may cause coma: (a) massive cerebral embolism to the unilateral carotid system particularly in dominant hemisphere (Plum and Posner) and (b) injection of phenobarbital into the carotid system of the dominant hemisphere briefly interrupts consciousness (Serafetenes et al). Clinical studies indicate that unconsciousness accompanies large hemispherical lesions, as well as small lesions critically located in or near the core of the brain stem tegmentum, rostral to the medulla.

It is uncertain whether or not destructive lesions confined to the medulla impair consciousness. Cairns (1952) and Jefferson (1944) thought that medullary lesions did cause coma, but they observed patients with expanding lesions that commonly exert widespread effects. Reichardt (1929) described a woman who apparently suffered a medullary puncture during a cisternal tap. She became unresponsive for 10 to 15 seconds but promptly recovered when the needle was withdrawn. The patient's condition was described and was reminiscent of syncope (her pulse slowed and the blood pressure was not taken). According to Plum and Posner (1966), medullary structures may exert relatively little direct effect on neural functions regulating consciousness. They described a man, age 62, who was alert and conscious until his death despite extensive destruction of the medulla by a hemorrhage extending rostrally throughout the medulla to its junction with the pons. Zulch (1965) considered that cerebellar pressure cone, with acute impaction of the medulla, produces severe autonomic symptoms with respiratory and circulatory arrest and loss of consciousness only as a secondary symptom. Some anatomicoclinical observations with well defined

The Blood Supply of the Brain Stem

and localized lesions, in which the assessment of the level of consciousness was based on combined clinical and electroencephalographic criteria, lead to the following conclusions:

Lesions located in the medulla oblongata and caudal pons, if compatible with survival, do not lower consciousness.

Lesions in the upper pons and caudal mesencephalon are often, but not always, followed by clinical signs of coma.

Lesions located in the rostral mesencephalon and in the diencephalon produce classical and complete clinical and electroencephalographic manifestations of coma.

On an anatomoclinical basis, the most caudal brain stem lesion, producing an *unequivocal* and *constant* impairment of consciousness, appears to be at the junction of the mesencephalon and diencephalon.

"Deactivating" mechanisms in man have not yet been demonstrated. Nevertheless, some anatomicoclinical observations and results of injection of barbiturates into the vertebral artery system seem to indicate their presence. Their precise anatomical identity is still uncertain.

Pathoanatomical Process Causing Disturbances of Consciousness

Expanding processes, producing impaction of the mesencephalon readily lead to intermittent or protracted disturbances of consciousness. Mesencephalic impaction tends to be characterized by *primary* unconsciousness, while impaction of the medulla (cerebellar pressure cones) produces unconsciousness as a *secondary* symptom (Zulch, 1965).

Can unconsciousness result exclusively from *severe intracranial pressure on the cortex* without brain stem infarction? The answer is negative.

Tumors

"Infiltrating tumors of the brain stem" caused disturbances of consciousness in 38% of 92 patients (Arseni, et al, 1959) and in 21 of 32 patients with tumors in the lower brain stem (Jefferson, 1952).

Two types of posterior fossa lesions cause coma. Those within the brain stem that *destroyed* the RF, and those outside the brain stem that *compressed* the reticulum.

Brain Stem Destruction

Lesions in the brain stem can cause coma, either directly invading and destroying the brain stem core (trauma, neoplasms) or by impairing its blood supply to produce necrosis, ischemia or hemorrhage (cerebrovascular disease). The most common pathological process that causes primary destruction of the brain stem is disease of the basilar artery. From the review of the vascular supply to the brain stem structure it is evident

that the blood supply to the RF and motor and sensory pathways is different. The paramedian (median) arteries and the lateral paramedian (short circumferential arteries) supply the reticular formation. The cerebellar arteries, superior and anterior inferior, supply important lateral structures mediating sensory and cerebellar functions, but do not participate in the supply of structures related to mammalian consciousness.

Posterior fossa lesions outside of the brain stem (e.g., tumor of acoustic nerve) can cause coma in three possible ways: (1) *direct compression* of the brain stem usually at pontine level; (2) *upward herniation* of the cerebellum and midbrain through the tentorial notch compressing the mesencephalic tegmentum, and (3) *downward herniation* of the cerebellar tonsils through the foramen magnum compressing the medulla.

Direct Compression

In posterior fossa tumors, just as with supratentorial lesions, the rate at which these changes develop has an important bearing on the severity of the symptoms. Large, rapidly developing masses, such as cerebellar hemorrhage, and rapidly developing postoperative edema, are frequently associated with coma. By contrast, slowly developing lesions sometimes reach greater size, producing extraordinary brain stem deformities without impairing consciousness. (In the case of acoustic neurinomas, the pons suffers primarily and becomes indented by the medium size tumors, but larger tumors may flatten it to half its size. The medulla also shares in the molding by these large tumors. The cerebellar distortion may be either insignificant or enormous, pushing the hemisphere backwards and upwards). However, sooner or later these may also compress blood vessels, producing ischemia and the aqueduct resulting in ventricular dilatation. Whichever the initial step, necrosis of both neural and vascular elements is the ultimate effect, with consequent development of coma and unconsciousness.

Upward Transtentorial Herniation

When the tissues in the posterior fossa expand selectively the cerebellum and mesencephalon may herniate through the tentorial gap, compressing the dorsal aspect of the mesencephalon, as well as its blood vessels and inducing changes in the midbrain and adjacent structures drained by the central cerebral veins. Upward herniation may also disturb the CSF flow by obstruction of the aqueduct and the pontine and ambient cisterns.

Lundberg (1960) recorded CSF ventricular pressure in patients with intracranial hypertension showing "obscuration" of consciousness or mesencephalic fits. Acute incarcerations of the brain stem coincide with considerable abrupt elevations of supratentorial pressure, causing the brain stem symptomatology. He considered that the trigger mechanism governing intracranial dynamics, under the conditions prevailing when the intracranial pressure is elevated, may be related to the underlying lesion or to a factor known to produce cerebral vasodilation or cerebral congestion (hypercapnia, Valsalva mechanism, painful stimuli, intratracheal intubation). He suggested that the plateau waves are caused by vasodilation produced by elevation of intracranial pressure.

The Blood Supply of the Brain Stem

Upward transtentorial herniation may also compress and distort the basal vein of Rosenthal and eventually the vein of Galen, raising the supratentorial venous pressure. Finally, the superior cerebellar artery may be compressed against the tentorial edge resulting in infarction of the cerebellum.

Upward transtentorial herniation occurs with expanding lesions of the posterior fossa. Vastine and Kinney (1927) reported upward displacement of the pineal body in 22% of 28 patients with acoustic tumors.

Ecker (1948) described a case of a 54-year-old man with an acoustic neurinoma who died after ventriculography. At autopsy, the acoustic tumor on the left measured 4.5 x 3.5 x 3 cm. It displaced the brain stem and the cerebellum to the right and upwards.

Downward Herniation Into the Foramen Magnum

This is a common terminal event in all cases of non-treated intracranial hypertension. Lesions in the posterior fossa (such as acoustic neurinoma, cerebellar neoplasms) may often produce this phenomenon. In patients with foramen magnum impaction due to tonsillar herniation, the medulla as well as the cerebellar tonsils became infarcted if they survived long enough. This extreme situation (it may occur during or in the postoperative period of acoustic neurinomas) rapidly produces severe autonomic symptomatology leading to fatal respiratory and circulatory arrest with equivocal morphological changes. The physiological mechanisms of coma in foraminal impaction is anoxia secondary to respiratory and circulatory changes, and not medullary compression *per se* (Plum and Posner, 1966; Zulch, 1965).

In posterior fossa lesions, it is difficult to separate the effects of direct brain stem compression from the effects produced by upward and downward herniation. All the three processes accompany almost every large lesion in this region.

Subtentorial (Posterior Fossa) Lesions Causing Coma Include:

(1) *Vascular Lesions:* basilar artery occlusion with pontine and midbrain infarction; primary pontine hemorrhage; cerebellar hemorrhage; vertebrobasilar aneurysm.

(2) *Non-vascular lesions compressing the brain stem (A rare cause of coma):* Cerebellar abscess ruptured into IV ventricle; granulomas; primary and secondary cerebellar neoplasms; extramedullary neoplasms (These rarely cause coma as an early sign, even if they distort, compress and displace the brain stem).

Summary

There are many implications arising from this review. Significant autonomic changes have been observed by surgeons during operations of acoustic tumors. These are a rise in blood pressure, respiratory and vasopressor disturbances, often transient, sometimes persistent and progressive. Occasionally, these are followed by disturbances of consciousness and, in a few instances, by coma and death. These changes have been

Bebin

attributed to spasm or occlusion of the anterior inferior cerebellar artery impairing the blood supply to the brain stem tegmentum and the structures and pathways subserving these functions. This theory has been partly supported by the postmortem findings in some of the cases studied by Atkinson and others. However, these findings have not been present in all the cases examined anatomically. Moreover, in the majority, the functional disturbances and the structural damage in the brain stem disclosed in neuropathological examination surpassed the territory supplied by a single artery. This suggests that an additional factor or factors: injury of the brain stem, hemorrhage, increased intracranial pressure, and anesthesia, play a role in the causality of the events observed during and after surgery. A prominent role seems to be played by the sudden rise of intracranial pressure. At first, the increased intracranial pressure is compensated by reactive vasodilatation but when the excessive pressure reaches a critical level (450 - 500 mm. H₂O) the cerebral blood flow cannot be compensated.

A further consequence is the development of the cerebral edema with distention of the ventricles, reduction of the cisterns, and mass displacement of brain tissue (herniations). This results in distortion and compression of the brain stem and circulatory disturbances (capillary and venule compression). The compression of large arteries may be so severe as to result in ischemia in the areas they supply.

Thus, all these events create the conditions for the development of vascular and respiratory disturbances which may lead to hypoxia, anoxia, cerebral edema, increased intracranial pressure. A vicious circle is perpetuated in this way and is only ended by death.

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