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PARADOXICAL SLEEP WITHOUT ATONIA

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INTRODUCTION

Certainly one of the most remarkable discoveries in neuroscience following Moruzzi and Magoun's revelation (41) of the key role that the reticular formation of the brainstem must play in arousal was the recognition only a few years later of a phase of sleep with characteristics strikingly different from those classically associated with sleep (2, 9, 10). The existence of rapid eye movement, desychronized or paradoxical sleep (PS) added an intriguing complexity to the concept of the ascending reticular activating system; for PS is characterized by EEG activity in the cortex and hippocampus similar to that of wakefulness. This demonstrates that the "arousal reaction" can not be equated with behavioral wakefulness (W). Of course, the tonic peripheral inhibition of motor activity during PS, so thoroughly explored in Pisa during the 1960's (44), effectively prevents the "arousal" of PS with its accompanying high level of activity in central motor areas from being translated into action and, not unreasonably, might be regarded as necessary for maintenance of PS. In fact, this is not so. The purpose of this essay is to examine the evidence for this last statement by reviewing the characteristics of a phenomenon that we have been studying for a number of years, paradoxical sleep without atonia (PS-A), and the important insights it has offered into the nature of PS.

MECHANISMS UNDERLYING PARADOXICAL SLEEP WITHOUT ATONIA

In 1965, Jouvet and Delorme (26) first demonstrated that the atonia of PS could be eliminated by bilateral electrolytic lesions placed in the pons, specifically referring the effect to damage of the locus ceruleus. Cats with such lesions did not exhibit PS for about three weeks when they then began to exhibit bouts of hallucinatory-like bahavior during sleep. The exact description of this historic finding seems worth repeating here.

"Chez trois animaux, vers le vingtieme jour, le tableau évolua: des périodes de type 'hallucinatoire' sont apparues. Elles surviennent à la fin d'une courte phase de sommeil lent. Les pointes monophasiques ponto-géniculo-occipitales tendent alors à augmenter et l'activité corticale peut être rapide. L'animal dont les pupilles sont en myosis et les membranes nictitantes relachées semble alors par-

ticiper à une scène onirique. Dressé sur ses pattes, il semble parfois lutter contre des ennemis imaginaires pendant plusieurs minutes. Son comportement évoque la rage et il semblerait totalement éveillé bien qu'il ne réagisse pas aux différentes stimulations sensorielles et que son comportement oculaire évoque le sommeil. Chez ces animaux, il ne fut jamais observé de veritable S.P. (sommeil paradoxal) avec abolition totale du tonus musculaire, activation corticale et phénomènes phasiques''.

We then replicated the phenomenon (18). It was clear to us, as well, that the episodes were best interpreted as PS in which the usual spinal motor neuronal inhibition (14, 32) had been lifted. Arguing in favor of this conclusion, in addition to the points made by Jouvet and Delorme (26), were the facts that intensity of movements waxed and waned as in normal PS; normal episodes never were interspersed with PS-A episodes; and recovery in some cats proceeded gradually with loss of tone and organized movements. In our paper we also added the observation that clear behavior that could be identified as PS -A emerged earlier than had been reported, within the first few days postoperatively. This suggested to us that delays in appearance of behavior probably depends upon nonspecific damage and reinstatement of adequate motor control should cerebellar damage be severe during passage of the pontine electrodes. Sastre (47) has also since observed PS-A behavior only a few days postoperatively.

Results of additional experiments by Hendricks *et al.* (17) indicated that the elaborate behavior observed during the altered PS state depended upon more than release from spinal motor neuronal inhibition (14, 32). Different lesion placements led to differences in the behaviors observed, indicating damage of different systems. Indeed, with experience I found it possible to predict either the lesion site or the behavioral syndrome from knowledge of the other. We identified four syndromes, but I now recognize that there are probably just two classes that have been revealed thus far, with three of the original groups just representing gradations of release from inhibition.

In the original formulation (36), Group I animals were those which exhibited what might be called «PS without atonia without behavior». Abnormally vigorous proximal movements occurred, but the head did not rise; and elaborate behavior did not appear. Nuchal EMG tone was recorded during much of each episode. Significantly, discrete bilateral destruction of only the medial locus ceruleus and medially adjacent reticular formation or bilaterally symmetrical, discrete lesions just medial to the motor nucleus of V produced this syndrome (Fig. 1). These lesions damage the origin or course of neurons contributing to the tegmentoreticular pathway described by Sakai *et al.* (46) and postulated by them to be the mediator of atonia. Work in decerebrate cats suggests that these neurons may be under the inhibitory control of elements in the more rostral locus ceruleus as classically defined (7,8). Obviously, additional damage must be done to produce more elaborate behavior.

Lesions extending more rostrally, ventrally or caudally resulted in much more dramatic behavior of the kind first reported (26). Cats demonstrating more elaborate

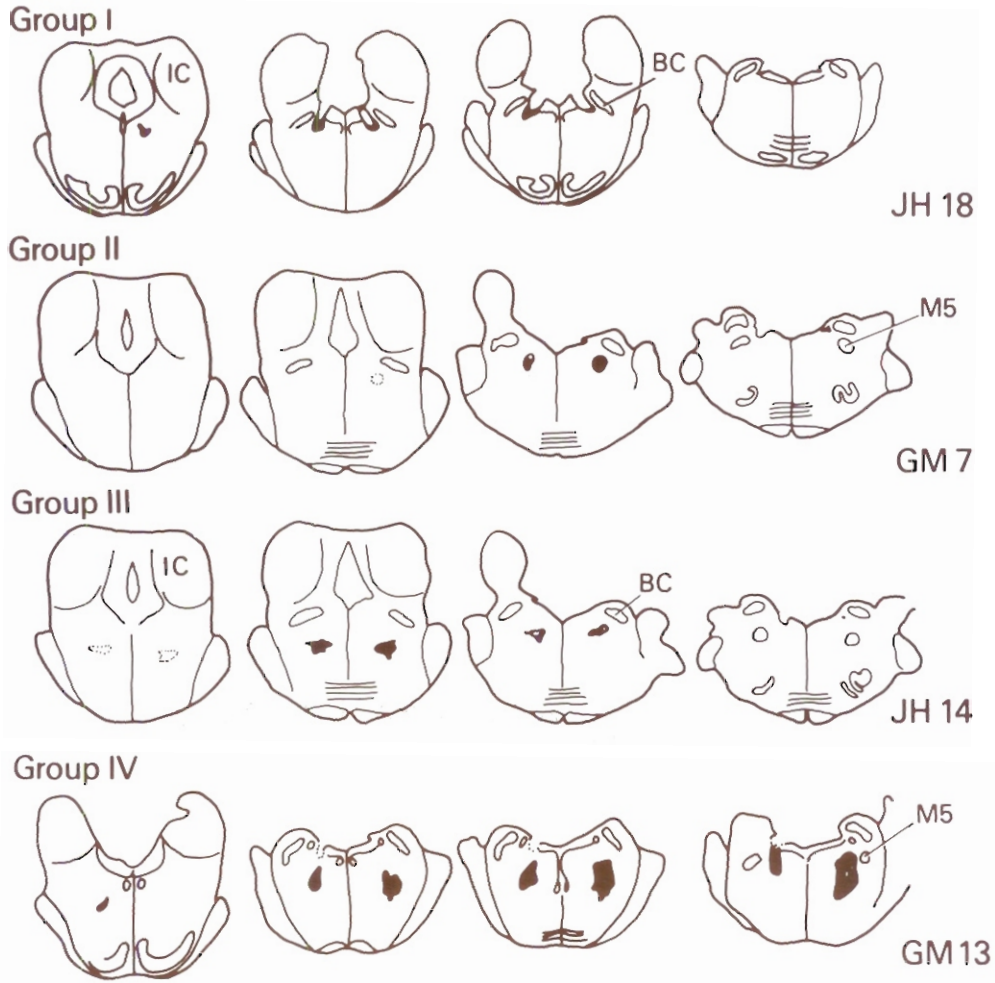

Fig. 1. — *Cross-sections drawn from cresyl violet-stained histological sections of brains with bilateral pontine lesions (black) that induced the various syndromes within PS-A.*

The rostral-most section of each series is at the left. Group I: nuchal muscle tone and excessive axial and proximal limb movements were present in PS but not head-lifting, body-righting or postural support. Attempts at head-lifting occurred, though, suggesting that insufficient anti-gravity muscle tone was released. This syndrome occurs with small or asymmetric lesions and in cases of recovery from the other syndromes. Group II: head-lifting, body-righting, partial to full forelimb support and orienting-like movements of the head occured. Group III: lesions that extended rostroventrally into the midbrain induced episodes of attack behavior, which resembled that seen in predation (28), in addition to the above. Group IV: such lesions, larger and extending more caudoventrally than the others, resulted in quadrupedal locomotion, although axial and hindlimb support were not complete. These cats also oriented and, if the lesion extended rostrally, attacked. Abbreviations: BC, brachium conjunctivum; IC, inferior colliculus; MV, motor nucleus of the trigeminal nerve. From Morrison (36).

behavior were placed into Groups II, III, IV (Fig. 1). Group II cats showed coordinated behavior involving the head, neck and forelimbs in movements resembling orienting, staring, searching, and attempts at standing. The smallest lesion needed to produce such behavior was symmetrical, centered at P3.0, L2.0 and V-3.0. Group III exhibited violent phasic behavior resembling attack punctuating tonic periods of quiet staring or searching movements. Attack resulted from damage extending rostroventrally into the midbrain. Group IV cats also had hindlimb support and locomoted quadrupedally although axial support was not normal; the animals would occasionally sink on their hindquarters (compare in Fig. 2 the cat in W (left) and the same cat in PS-A).

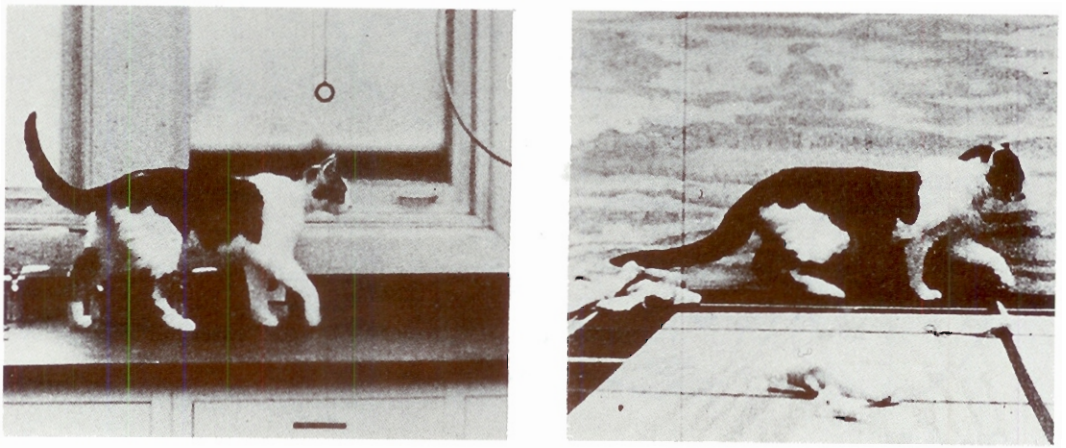

Fig. 2. — *The same cat in wakefulness (left) and PS-A (right).*

The lesion was of the Group IV type in Fig. 1. Although normal cats will walk with a crouch in W, a fully erect posture was never seen in PS-A due to the incomplete release of axial and limb extensor muscle tone. Poor proprioceptive placing, as measured by lateral sliding of a limb when stepping on a smooth surface, was also a feature. From Morrison (37).

In these latter three groups asymmetrical lesions resulted in temporary (2 to 12 weeks) elaborate behavior, with recovery to the Group I syndrome. Otherwise, PS-A probably can supplant normal PS indefinitely since we have kept cats almost a year before euthanizing them. All lesions extending rostrally into the midbrain resulted in attack behavior during PS-A. A subset of cats demonstrating attack behavior had asymmetrical pontine lesions that unilaterally involved a descending pathway from the central amygdalar nucleus (22).

Because different lesions resulted in predictably different behavioral syndromes during PS-A, we have reasoned that the cats are not simply expressing the neural activity of normal PS, or cat dreams if you will. At least two systems must be involved by the lesions, and probably more.

It is clear now that groups I, II and IV simply represent different degrees of release from motor inhibition and that group III attack behavior depends on

sufficient release from motor inhibition to support the coordinated attack sequences freed by additional damage of unidentified structures rostroventrally. Historically, this interesting group (of which more will be said later) was recognized early in our work; whereas group IV only emerged as we made much larger lesions, which are necessary to obtain the fullest release of antigravity muscle tone and, therefore, quadrupedal locomotion.

Exactly which neurons, or systems of neurons, must be destroyed to induce group IV behavior has been a subject of continued debate. Initially, the noradrenergic neurons of the caudal locus ceruleus seemed appropriate candidates (26). The fact that neurons presumed to be noradrenergic neurons were later found to fall silent in PS (6, 21) rendered this possibility unlikely. Our later demonstration (17) that lesion site and size could be correlated with qualitative differences in behavior argued further against a single neuronal group. Furthermore, other aspects of the cats' behavior suggested that PS-A might involve more complex derangements of motor control than simple removal of supraspinal inhibition of motor neurons.

In W the cats demonstrated a significant increase in open-field locomotion (39). This observation prompted me (35) to consider the possibility that the tegmental lesions were removing other inhibitory influences as well, the most obvious being those inhibiting mechanisms organizing and driving coordinated movements. This thought was prompted by the proximity of the lesions to a region (Fig. 3) lying just ventrally to the inferior colliculus and dorsally to the brachium conjunctivum, which projects caudally through a region lateral to our lesion site (34). Called the mesencephalic locomotor region (MLR), this area when stimulated electrically will drive walking, trotting or galloping movements of acutely decerebrated cats that would not ordinarily locomote on a treadmill.

Our recent experiments (40) have strengthened that early hypothesis, which was admittedly speculative and based primarily on intuition. Among the refinements to our understanding of the MLR and its interactions with the neurons that must organize as a spinal locomotor apparatus has been the demonstration by Mori's group that pontine structures can profoundly influence effects obtained by MLR stimulation (33). Specifically, electrical stimulation of a dorsal midline pontine region extending from P3 to P7 will inhibit treadmill locomotion of decerebrate cats induced by MLR stimulations as well as spontaneous free-ranging locomotion of intact cats (Fig. 4, top). Conversely, more ventral midline stimulation alone will induce locomotion on a treadmill and cause an intact cat to rise from a recumbent position and walk. We reasoned that, if PS-A involved more than the simple destruction of a localized group of cells in the dorsal pons, then a lesion placed in Mori's dorsal midline inhibitory area could be expected to enhance behavior during PS-A.

In cats already exhibiting PS-A motor release to varying degrees, we added a second dorsal pontine midline electrolytic or cytotoxic (ibotenic acid) lesion (Fig. 4, bottom) at least eight weeks later because full development of quadrupedal locomotion can require that lenght of time to develop. We tested whether or

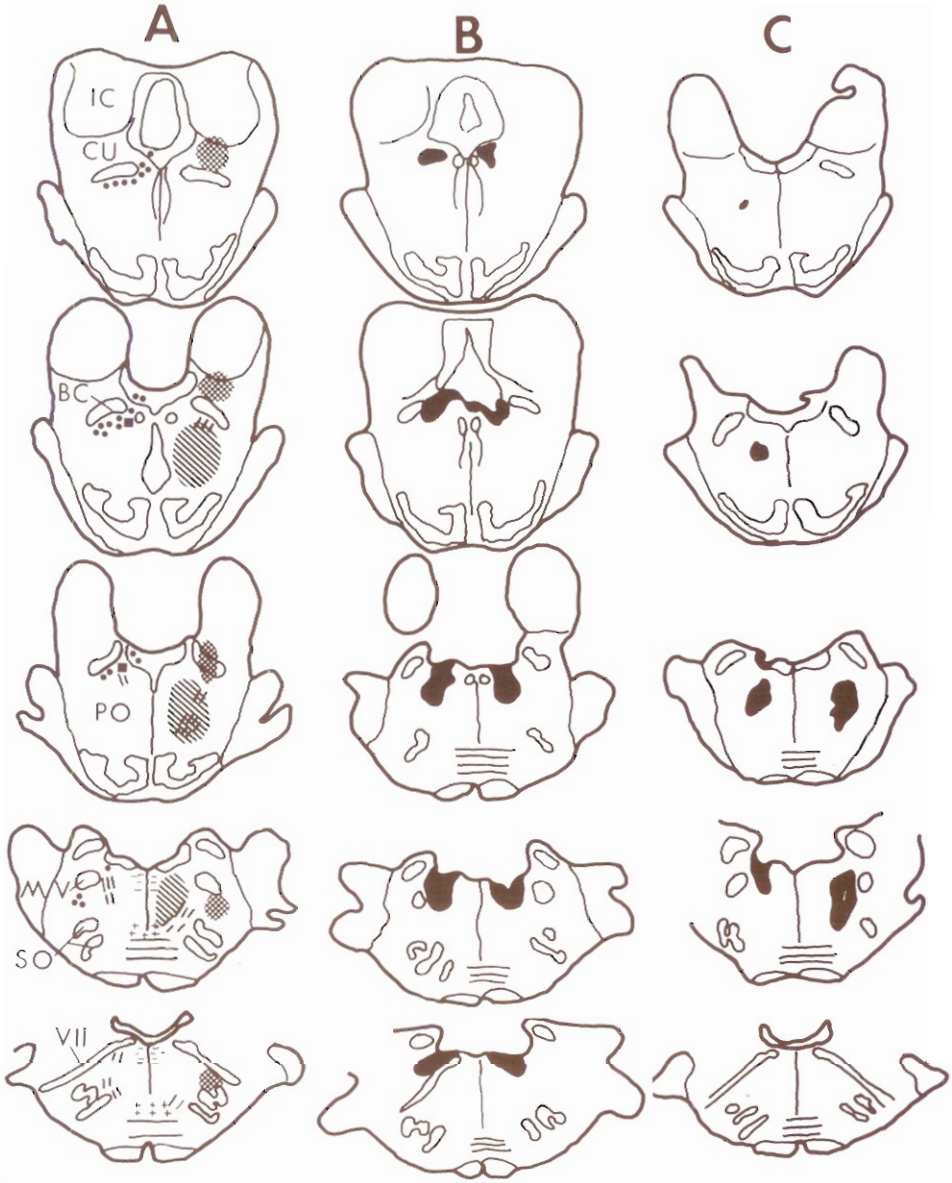

Fig. 3. — *Structures involved in different aspects of PS-A.*

A: structures possibly involved in PS-A shown on cross-sections of the pons, the most rostral being at the top. See text for details. B: cross-sections illustrating a rostral lesion (black) that induced forelimb support and considerable orienting in PS-A. C: cross-sections illustrating a caudal lesion (black) that induced quadrupedal locomotion. Symbols in A: left-open circles, cells projecting to the deep layers of the superior colliculus (11); closed squares and dashes, origin and course of the tegmento-reticular tract, destruction of which Sakai *et al.* (46) suggest leads to all behavior in PS-A. Midline: minuses, region that when stimulated electrically inhibits extensor tone and movement during treadmill locomotion of decerebrates (33); pluses, region that when stimulated electrically increases extensor tone and can initiate locomotion (33). Right: cross-hatching, origin (mesencephalic locomotor region) and course of the pontobulbar locomotor strip (34); dashes, projection from the mesencephalic locomotor region to the midline facilitatory area (13); hatched zone, area affected by C-type lesions and also containing cells projecting to and /or through the midline inhibitory area (Mori *et al.*, personal communication). Abbreviations: BC, brachium conjuctivum; CU, a cuneiform nucleus; IC, inferior colliculus; MV, motor nucleus of trigeminal nerve; PO, nucleus reticularis pontis oralis; SO, superior olivary complex VII, facial nerve. From Morrison (37).

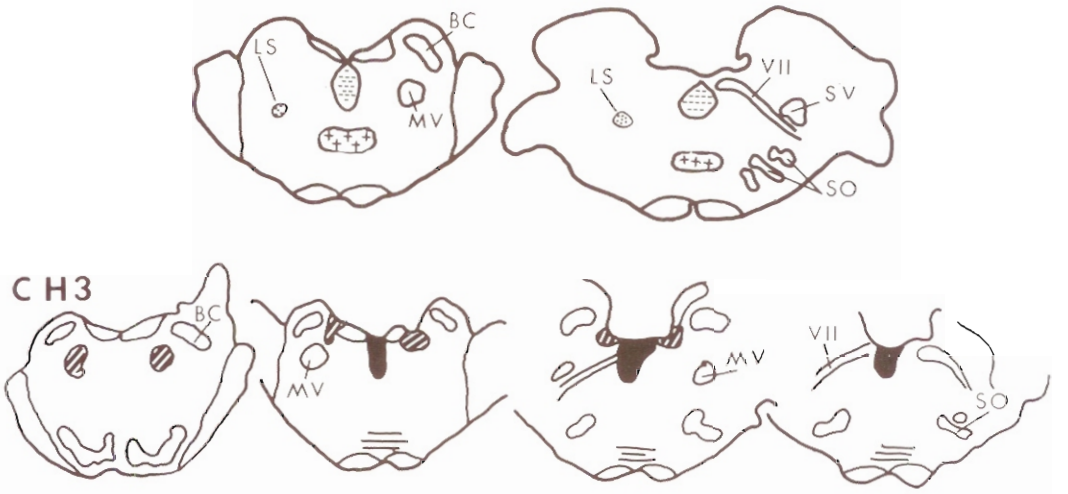

Fig. 4. — *Brainstem cross-sections.*

Above: lateral locomotor strip (dots), midline inhibitory (—) and facilitatory (+) areas (see ref. 33) Below: lateral (hatched) and midline lesions (black) in i cat. Abbreviations: BC, brachium conjunctivum; VII, facial nerve; LS, lateral locomotor strip; MV, motor nucleus of Vth; SO, superior olivary nuclei; SV, sensory nucleus of Vth.

not removal of the inhibitory area would lead to more elaborate behavior in PS-A, specifically that a group II animal with forelimb support alone might be converted into a quadrupedally locomoting group IV cat. Although the results were not that dramatic in every case, two of the five cats with electrolytic lesions were converted from group II to group IV behavior. The others exhibited a significant increase in limb movements counted during the first three minutes of several videotaped PS-A episodes (Fig. 5). The effect appears due primarily to interruption of fibers passing through this sparsely cellular region, for ibotenic acid injections gave inconsistent results in three cats — no effect, an increase and a decrease in PS limb movements.

At the moment the most likely explanation for the different effects from lateral lesions is that they depend upon bilateral damage of neurons in nuclei reticularis pontis oralis to varying degrees, the more extensive the damage the greater the release as is illustrated in Figure 3. Only forequarter support occurred during PS without atonia after the Figure 3 B lesion, whereas quadrupedal locomotion followed that depicted in C. Although we initially thought (40) that the midline lesions might be interrupting crossing reticulo-reticular fibers that might then excite the medullary inhibitory area via caudually directed neurons, recent work by Mori *et al.* (personal communication) suggests that their stimulation and our lesion effects are due to a bilateral, reasonably symmetrical impingement on medial, caudally coursing axons from pontis oralis. Note also in Figure 4 that two pathways capable of driving locomotion extend caudally from MLR (13) so that even partial

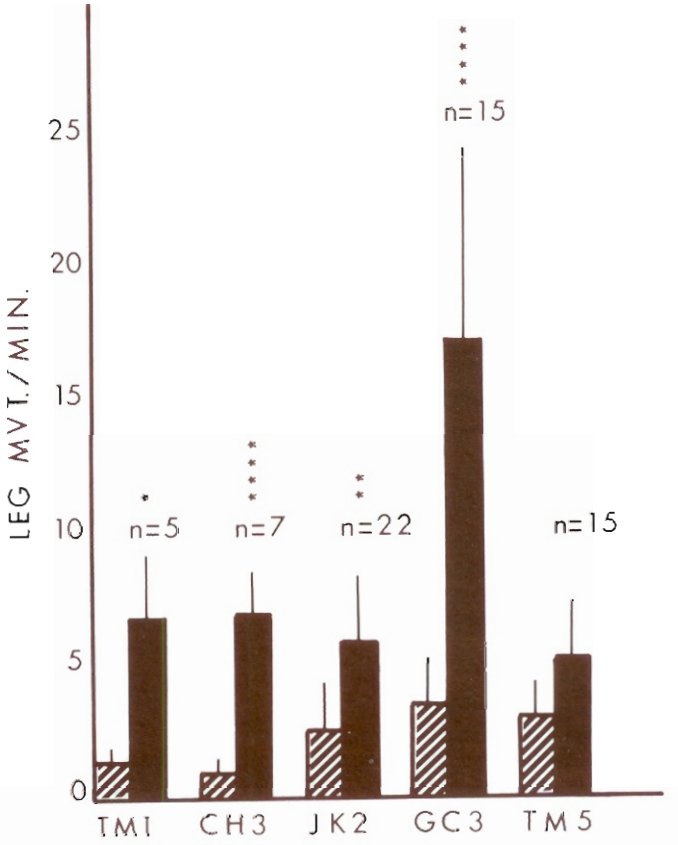

Fig. 5. — *This graph demonstrates that electrolytic midline lesions (black columns) significantly increased limb movements in PS-A episodes induced by prior lateral lesions (hatched columns) in all but TM5 ("N" signifies number of PS episodes analyzed).*

TM5, as well as CH3, were converted from exhibiting only forelimb support in PS-A to quadrupedal locomotion. JK2 and GC3 were already walking quadrupedally.

destruction of the medially directed one which excites Mori's ventral facilitatory area, would leave untouched the earlier described lateral pathway (34).

The presence of these two parallel caudally projecting brainstem pathways that are capable of orchestrating locomotion in cats enables one to understand a current discrepancy in the literature. The idea that pontine tegmental lesions will eliminate PS, first proposed by Jouvet (25), has reappeared, although cats in that study had actually displayed PS-A (see ref. 18 for discussion). Jones and Friedman (12, 24) have reopened the case with their observation, bolstered by sophisticated computer analyses, that clear evidence of PS (appropriate combination of low EEG and EMG amplitudes with high PGO spiking) was no longer present after either caudal pontine lesions extending across the mediolateral extent of the tegmentum or lateral, caudal pontine lesions alone, noting that they had confirmed Jou-

vet's (25) early work, which, as I have noted, did not actually eliminate PS. They did not detect the elaborate behavior of orienting movements and locomotion that one sees in PS-A with more rostral lesions.

At first glance, their results are difficult to understand in view of the fact that complete transections through the caudal pons still permit rostral signs of PS as judged by PGO spiking, rapid eye movements and low EEG amplitudes although EMG of facial muscles remains and the state occurs at longer intervals than normal (49). Thermal lesions would destroy more tissue rostracaudally than would transections, however, which could explain the discrepancy. Also their two lateral caudal lesions that purportedly eliminated PS may have involved enough of the lateral pontobulbar path extending from the MLR (13, 34) to prevent expression of behavior during PS-A. They do not report if the amount of locomotion in W were changed but do describe that the cats walked with head down and limbs flexed, suggestive of motor control inadequate to support PS-A behavior.

The PS-A preparation now forces us to do more than note in passing what sleep researchers have long recognized: the fact that PS represents periodic occurrence of brain activity during sleep that possesses so many characteristics of alert W but which does not arouse the cat to action as in W. Cats will remain in PS-A for many minutes while walking and engaging in behavior that resembles slow searching or even rapid orienting movements. Thus, we must conclude that even though the usual atonia has an obviously useful protective function, peripheral motor inhibition is not a highly significant factor in maintenance of PS.

What mechanisms, then, are critical for maintenance of sleep during the PS phase? Transmission at the periphery is depressed, but sensory regions more centrally are not (44). Nevertheless, cats in PS-A that seem to be responding to centrally generated stimulation do not translate this into full interaction with their environment. Silence of the ubiquitously projecting noradrenergic neurons of the locus ceruleus, which may be significant in giving human dreams their bizarre quality (19), may also render the PS-A central stimulation insignificant and incapable of arousing the cat to useful activity. We have preliminary evidence based on a few neurons recorded from the locus ceruleus indicating that these cells are silent in PS-A as they are in normal PS (6, 21, 45), unlike serotonergic dorsal raphe neurons that are reactivated during PS-A (52) [1].

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[1] The fact that serotonergic neurons in the dorsal raphe nucleus resume firing in PS-A (52) is a very significant finding, for it clearly challenges the assertion that silence of these neurons is contributory to the onset of PS, a tenet of the "reciprocal interaction" model of sleep state control (20). In seeking to define what characteristic(s) of PS affected by the lesions might normally be responsible for dorsal raphe inactivity, we unfortunately chose the word "atonia" when, in fact, "central motor inhibition" would have been more accurate. Lydic et al. (29) later found that decrease in dorsal raphe firing and muscle atonia are not strictly correlated and, therefore, discounted feedback from muscle activity as a controlling factor in the regulation of dorsal raphe firing. This is probably correct, but they stopped too soon in responding to the challenge of our data (52). Stimulated by those data, Steinfels et al. (51) demonstrated that dorsal raphe discharge is unaffected by peripherally paralyzing agents but ceases upon pontine injections of carbachol. The latter occurs even if the cat is paralyzed *but awake* as determined by facial flinch responses to threat and following movements of the eyes. This result would seem to argue against inclusion of dorsal raphe neurons as part of the controlling mechanism of PS (20).

Another mechanism limiting reaction to reticular activity may be inhibition of the waking function of the superior colliculus (SC). SC is a key integrative structure involved in an animal's detection of and orientation to a variety of stimuli, not just visual (50). Its most superficial layers receive retinal information; but intermediate and deep layers receive other input from both sensory and motor structures throughout the neuraxis; and these are highly organized into modular groupings with efferent neurons that distribute to nuclei that can generate appropriate orienting movements of the head and neck (23). These efferent neurons receive multimodal sensory information as well (30). Initially after bilateral SC lesions, cats appear blind and respond sluggishly to tactual and auditory stimuli (50). Chronically they neglect stimuli in upper and lateral visual fields and have poor tactile localization on the hindlimbs. Ipsilateral lesions induce ipsiversive circling and contralateral neglect that chronically resolves to attending preferentially to ipsilateral stimuli and to losing objects moving in the contralateral visual field. We suggest that in addition to participating in the generation of motor inhibition, the rostral dorsal pontine tegmentum may have the capability of inactivating the SC during PS, which, by functionally mimicking the early effects of bilateral SC lesions (50), renders a cat less responsive to the activating influences of a reticular formation that is in an "orienting mode".

Edwards *et al.* (11) have shown that the rostral dorsal pontine tegmentum projects to SC (Fig. 4). Other workers have found that carbachol injection in that area, just ventral to the periaqueductal grey, rendered a cat completely unresponsive as well as atonic and incapable of righting (27). After righting and postural support had returned, orienting to stimuli was still lacking, even though the eyes blinked to bright light or threat and followed. Injections more ventrally induced PS from which cats could be aroused, as had been well-documented earlier (20).

Cats with caudal, even quite large, lesions walk in PS-A; they appear to have longer, less disrupted episodes than those with more rostral lesions that involve the SC projection zone (Fig. 4), although we have not quantitated this impression yet. With only partial destruction of the (potential) inhibitory zone projecting to SC, cats with lesions as in B might react to internal stimulation during PS-A at a level sufficient to arouse them at least part of the time. An obvious test of this hypothesis would be addition of bilateral SC destruction subsequent to the pontine lesions depicted in B. One would predict a reduction in orienting-like movements and longer PS-A episodes.

PS-A is more than just a spectacular phenomenon. It has, of course, provided insights into the inhibitory processes of PS; but it has done much more as well, proving itself to be the useful research tool we earlier predicted it would be (38). For example, PS-A has provided a striking demonstration of the depressed thermoregulation of PS (43). During PS-A cats shivering violently during W and SWS at an ambient temperature of 10° C ceased shivering completely in PS-A (15), despite the fact that cats with such lesions are actually more sensitive to cold and heat in W (1). What is most significant about the results of these experiments to me is the fact that while motor inhibition is not a critical, or at least a necessary

feature of PS, suppression of homeostatic regulation (as exemplified by depressed thermoregulation at least) is more fundamental. I suspect that reduced homeostasis is probably a necessary feature of PS.

We have used PS-A to study aggression as well (Washington and Morrison, unpublished observations). Our results differ from other reports in two significant ways. In the first place, aggressive-like behavior was not an inevitable feature of PS-A as one might gather from the original description quoted above (26) and later work (47, 48). Of 28 cats with PS-A that were studied, only eight exhibited the "aggressive" syndrome. This result provides strong support for our claim (17) that behaviors released in PS without atonia depend on more than elimination of atonia for their expression; another system modulating aggressive behavior must have been damaged in these cats with rostrally extending lesions.

Secondly, the aggressive behavior displayed in PS-A resembled that seen in predation: ears pricked, batting with the forepaws, sometimes a terminating bite (28). No affective signs were observed except sometimes at the time of arousal. Six of the eight cats were also aggressive in W, but there was a striking difference. They showed absolutely no change from their *prelesion* encounters with live mice (no killing or nor increase), but they became very aggressive toward other cats to whom they had been either neutral or friendly when placed together in an observation room familiar to both. There was a strong affective component, including ear-flattening and hissing. The peculiar head-cocked stalk with vocalization more typical of inter-male aggression also occurred. Cats with lesions had to be restrained from inflicting actual physical damage on the normal member of the pair. Although two of the cats would attack the experimenter spontaneously and thus became dangerous, the others could be handled without fear. They might unexpectedly strike or bite mildly while being examined, but there was not the full development of attack that would preclude handling. This behavior struck us as being offensive in nature though.

Two obvious differences between W and PS-A might account for the change in expression of "aggressive" behavior between the two states. Most assuredly the cats experienced reduced environmental stimulation during PS-A. Equally important, we think, is the greatly reduced sympathetic tone that characterizes PS-A (relaxed nictitating membranes; failure to piloerect in the cold (15). In other words, the peripheral apparatus necessary for the the expression of affective behavior is generally unavailable.

This has very important implications for research on neural systems involved in modulation of aggressive behavior. It suggests that to act "angry" a cat has to "feel angry". It suggests that the brain must receive information that there is an output to the visceral organs either from central feedback from within the brain, an efferent copy, or via afferents from the periphery. The latter cannot happen in PS-A due to reduced sympathetic activity (5), and it seems unlikely that the former would either, given the reduction in hypothalamic control during PS (43). This proposal does not really reinject the concept of vague mood to which modern workers in aggression object (4); but rather, it acknowledges that

more emphasis should be placed on the fact that input from visceral structures (3), or central feedback from efferents to them, can have a level-setting effect on the ultimate expression of aggressive behavior like that provided by the visual and somesthetic systems (4) and hormonal state (42).

Most recently PS-A has been used to examine the significance of diaphragmatic inhibition during PS (Hendricks, Klein, Davies and Pack, unpublished observations). The inspiratory slope of diaphragmatic activity during PS measured on a moving-average of the electromyogram (DIA ma) is consistently increased after pontine lesions. The difference was highly significant when the average DIA ma in PS in the same cats before lesions ($p < 0.00001$, 2 way ANOVA). The dorsal tegmental damage also abolished brief (40 ms) complete inhibitions in inspiratory diaphragmatic activity, which normally occur during 4-7% of breaths in PS. The area lesioned thus appears to be responsible for both an average reduction in inspiratory drive during the entirety of PS and also for brief complete suppressions lasting approximately 40 ms.

These two forms of inhibition may impair ventilation and predispose the animal to hypopneas during PS. In fact, studies of the English bulldog, an animal with upper airway obstruction and sleep-disordered breathing, have shown that inhibition of the diaphragm predicts oxyhemoglobin desaturation more reliably than inhibition of upper airway muscles. In more than 20 episodes of desaturation recorded during PS, diaphragm inhibition preceded every episode; while upper airway muscle activity was variable (16).

CONCLUSIONS

PS-A is a remarkable and powerful phenomenon. It is easily induced in cats, our success rate being approximately 80%; and it has been demonstrated in rats (31). The foregoing has demonstrated that, when used as an experimental tool, PS-A has contributed significant insights into the nature of PS. It can do more. It should prove useful in learning and memory experiments, or whenever one wishes to study motor output of the brain in a state of central excitation largely divorced from environmental influences.

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