PARESTHESIA IN A RHESUS MONKEY ASSOCIATED WITH A THALAMIC LESION, AND ITS ALLEVIATION BY POSTCENTRAL CORTICAL EXCISION*

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Roussy (1) described the thalamic syndrome in 1907, and reported the results of his studies on a variety of animals subjected to electrolytic lesions of the thalamus. In these animals he saw the hemianesthesia, hemiataxia and hemiplegia which were features of his "thalamic syndrome" in the human, but he did not describe the painful paresthesias and the choreo-athetoid movements that completed the picture. Dusser de Barenne and Sager (2) later described the transient hyperesthesias, hyperalgesias and (probably) painful paresthesias that could be observed in experimental animals following intrathalamic injections of solutions of strychnine. These symptoms disappeared with the disappearance of the drug, and a review of the literature on the experimental production of persisting painful paresthesias indicates that such reports are rare. Accounts of the physiologic effects of experimental thalamic lesions created for various purposes [Patton, Ruch, and Walker (3)] describe no behavior suggesting the presence of such symptoms, and in our own laboratories electrolytic lesions in the thalami of many carnivores and primates have never produced them.

This paper reports the appearance of persisting, apparently painful paresthesia in a rhesus monkey following an experimental thalamic lesion containing alumina cream, and the effect of postcentral cortical excision on the symptom.

PROTOCOL

J640 was a large (5,000 gm.) old, female rhesus with a corneal opacity and cataract of the right eye.1

On November 17, 1947, she was anesthetized (Versedal 120 mg. intramuscularly and 30 mg. intravenously) and through a small trephine opening 0.65 cc. of alumina cream2 was

* Aided by a grant (RG 514) from the United States Public Health Service.
1 The monkey came from the animal colony in the Department of Neurology, College of Physicians and Surgeons, Columbia University. There was no information concerning its previous use for experimental purposes and its behavior has been normal for at least three months prior to this study. As a pilot animal it preceded a series of monkeys subjected to similar stereotaxic injection in a variety of subcortical sites, part of a study on the experimental production of epilepsy carried out in the Department of Bacteriology, Psychiatric Institute, New York. The study of physiologic effects in this series of monkeys is currently in progress.
2 The alumina cream was prepared by adding a slight excess of 1 per cent ammonium hydroxide at room temperature to a 1 per cent solution of ammonium alum. The resulting precipitate was washed by decantation until only traces of sulfate remained in the supernatant fluid, and the centrifuged precipitate was injected as alumina cream.
injected into the left thalamus through a 21 gauge needle oriented by the Horsley-Clarke stereotaxic apparatus. She appeared normal on the following day.

December 6. The animal was observed to bite once at the dorsum of her left forearm. No hyperesthesia could be demonstrated in this area. Daily observation prior to this date had disclosed no abnormalities in behavior. During the next week the animal was observed to bite frequently at the dorsum of each forearm and at the central aspect of each wrist. The biting was more frequent on the right. Occasionally she bit at the dorsum of the right foot. During an environmental irritation or during excitement frequency of biting increased to 8-10 times per minute. The general pattern of "biting" was stereotype. While sitting quietly in her cage she suddenly "started", making one or two generalized tonic movements, and emitting several explosive squeals. She then bit one or another of the extremities. The duration of the entire sequence was one or two seconds. On one occasion (during cinematography) the animal danced about on one leg, holding the opposite foot in both hands as though she had dropped something heavy on her toes. There was, however, no subsequent "favoring" of the foot during progression. Sometimes, after biting, she studied the affected areas intently. She became very irritable, snarling and striking aggressive poses upon the slightest provocation. Minor stimuli such as sudden noises in the animal house or a slight blow upon the cage wall would immediately precipitate an attack of biting and squealing.

December 21. The monkey bit at folds between the toes, at the dorsum of each foot, at the knees, and at the tail, as well as at the sites described above. The wrist and ankles became hairless over the bitten regions, but no gross skin lesions or trophic changes were apparent. During the next three weeks the symptoms persisted unabated.

January 13, 1928. General examination on this date revealed that the patellar reflexes were of high threshold but normal in zone, latency and other characteristics. Painful stimuli were well perceived everywhere and no hyperalgia could be demonstrated. The animal did not "start" or bite while under examination.

With the animal under Dial-aether and Nembutal anesthesia the motor cortex was identified by electrical stimulation and an area extending 1 cm. posterior to the central sulci was excised with a scalpel to the depth of white matter (0.5 cm.) (fig. 1). Bleeding was controlled with the electrocoagulator. The excision extended from the callosum to a point on the lateral surface of the hemisphere 1.5 cm. from the midline. Beneath the edge of the dura along the postero-inferior margin of the excision an area of soft brownish cortex was seen. (There was no evidence on the skin or skull of injury or of previous experimental entry.) After operation, metrazol (0.5 cc.) and penicillin (15,000 U. in xyn) were injected intramuscularly and the animal was placed in an incubator.

January 16. The animal exhibited a left hemiparesis with slight semiflexion at the elbow but was able to move all its extremities. The thresholds for painful stimuli and latency in responses were bilaterally equal. In the afternoon the animal was able to sit but was not seen to walk, and required assistance in feeding.

January 17. The animal had eaten food during the night and was returned to her regular cage. She moved about in a fairly normal fashion and used the extremities on the left in walking and feeding but not in grooming. On three occasions, when excited, she raised her left hand to her mouth in the old manner but performed the action slowly and did not complete the act of biting the wrist. The left wrist was the only part bitten in this abortive fashion during three 15 min. periods of observation.

January 19. The animal's behavior was normal. She showed a preference for the right hand in feeding. She bit at both wrists with equal frequency but not at other sites.

January 23. The animal was carefully examined under light Nembutal narcosis to obviate the inconsistencies in sensory examination associated with rhesus somnolence. After a normal latent period she responded to slight painful stimuli of normal threshold everywhere (e.g. tugging of hairs, repeated needle pricks). The left patellar, biceps and radioadductor reflexes were of higher thresholds than those on the right and the movements were more pendular, but the reflex characteristics otherwise were normal. There was no ab-
normal resistance to passive movement and no weakness was demonstrable despite the earlier hemiparesis. During the next several days the animal was observed to bite at each extremity upon occasion, not less frequently than before, and no difference in the frequency of biting was noted between one side and the other.

January 28. Examination revealed no abnormalities of motor, sensory or reflex function. With the animal under "Nembutal" anesthesia, the lateral aspect of the cerebral cortex was exposed on the left. Attempts to determine the motor area of the cortex were unsuccessful. An area of cortex was excised extending 1 cm. posterior to the central sulcus and laterally from the extremities of this incision for a distance of 2 cm. (fig. 1). Metrazol (0.75 cc.) and penicillin (250,000 U. in wax) was injected intramuscularly, and the animal placed in the incubator. On the following morning she was alert and moved around spontaneously. The extremities on the right were mildly parietic but were used in climbing and walking. She showed a preference for the left hand during feeding. Painful stimuli were perceived equally well everywhere. She could not be induced to bite at any of her extremities by irritation or sudden noises.

February 1. No finger movements were observed in the right parietic hand on this date. During the next few days, however, the hemiparesis improved markedly. The left hand was still employed exclusively in reaching and feeding. The right was moved at the shoulder during quadrupedal progression and supported weight, but otherwise it hung at the animal's side. On one occasion it was suddenly raised toward the animal's mouth, as though about to be bitten, but the act was not completed. This was the most rapid movement made with this arm. During observations repeated several times daily and until sacrifice, 26 days later, the animal was seen to bite in the usual manner at the left upper extremity, but much less frequently than before. On two occasions she bit at the left leg, but she did not bite at any of the other sites. The generalized "startings" persisted but were less frequent than prior to the second operation.

The left hand showed a tendency to overshoot its mark when reaching for an object, and at times parakinesis of the upper arm and shoulder were apparently part of an activity compensating for this dysmetria. She had become much more placid after the second cortical operation. Episodes of snarling and the assumption of aggressive poses were less frequent.

February 21. The animal utilized all four extremities in getting about the floor of the laboratory. The right arm was employed as frequently as the left while the animal was climbing and in the forceful gripping of objects, but showed some weakness and frequently hung limply while feeding progressed with the left hand. There was considerable weakness in both lower extremities, evidenced by the animal's failure to raise its hips more than 3-4 cm. from the floor during progression, but no adductor hypertonus was present. Upon examination, cranial nerve innervation was intact. The slight weakness in the right upper extremity was confirmed, and a moderate hypertonus was demonstrated about the elbow and shoulder in this upper extremity, and about the knee on this side. The animal withdrew the left hand and foot sooner and more rapidly from a stimulus of repeated pinpricks, or from squeezing of the interdigital folds. Withdrawal of the face from pin prick was performed with equal speed and at the same threshold on right and left. The patellar reflexes were of normal zone, threshold, and latency bilaterally, with reflex contractions of good force and amplitude, and rapid maturation. On the right, the quality was more pendular than on the left. On the left and right, the hallux was flexed and the limb withdrawn upon plantar stimulation, and a phenomenon which had not been present before was noted, namely that the hallux exhibited repeated "click-like" flexions of small amplitude as long as the stimulus was applied. This was somewhat more marked on the right.

February 26. Repeated examination confirmed the findings on February 21 in every detail, and the animal was sacrificed on this date. Its weight was 4.5 kilograms, crown-rump length was 15 cm., and rectal temperature was 100.5 degrees Fahrenheit.

Summary of protocol: Three weeks after unilateral intrathalamic injection of alumina cream, a rhesus monkey developed apparently painful paresthesias characterized by
paroxysms of starting and squealing, and by biting at sites on the body surface bilaterally. The symptoms persisted 14 weeks, and diminished markedly during the four weeks following completion of two-stage excision of postcentral cortex.

Necropsy disclosed nothing of note in the internal organs. The brain and segments of the spinal cord were placed in 10% formalin.

The Brain: Cortical lesions: The extent of cortex excised on the left measured 5 mm., along the depths of the great longitudinal fissure posterior to its junction with the central sulcus. It extended down the lateral cerebral surface for 23 mm., was bounded by the posterior wall of the precentral gyrus anteriorly, and across its most lateral extent, measured 8 mm. (fig. 1). Its base was white matter. Extending posteriorly and ventrally from its postero-inferior aspect was the surface lesion noted during the first cortical operation. This continued for 20 mm. further down the lateral aspect of the cerebrum and measured 10 mm. in antero-posterior width. It was placed across the gyri of the temporal lobe as they join the parietal and occipital regions. Its base at a depth of 2 to 3 mm. was friable, and its margins were irregular.

Fig. 1. The gross appearance of the formalin-fixed brain of J.E.O., seen from the left, from above, and from the right.

The cortex excised on the left measured 9 mm. in width posterior to the central sulcus, and the excision began parallel to the great longitudinal sulcus, but 8 mm. lateral to it. It extended down the lateral cerebral surface for 21 mm., was bounded anteriorly by the posterior wall of the precentral gyrus, and posteriorly by the excision line, which was 4 mm. from the anterior margin of the lesion in its most inferior part. The lesion on the left therefore extended twice as far down the surface of the cerebrum as did the lesion on the right, but fell short of the midline by 8 mm., while that on the right included tissue along the wall of the superior longitudinal sulcus.

Subcortical lesions: Upon section of the fixed brain, through levels exposing the posterior part of the thalamus above the subthalamic nuclei and substantia nigra, a reddish brown lesion appeared in the thalamic region on the left (fig. 2). Its medial margin was 2 mm. from the midline. Its greatest diameter was 4 mm. and its width at this diameter's midpoint was 2 mm. It was roughly reniform with its hilum facing ventro-laterally. The hilum was apparently formed of uncolored tissue extending as a crescent into the discoloration of the lesion.

Microscopic observations: Blocks of tissue containing the cortical lesions and sections through the thalamic lesion were prepared and stained by the method of Nissl.

A needle track traversed the internal medullary thalamic lamina on the left, and sank into the lateral part of the medial nucleus as it approached the site of the thalamic lesion.
The needle track enlarged rapidly at the level of the mammillary bodies, in the position of the centromedian and parafascicular nuclei, and the lesion destroyed most of these nuclear masses. It extended into the adjacent medial and dorsal parts of the arcuate nucleus and the lateral nucleus of the lateral part of the thalamus at this level.

The lesion measured 3.5 mm. in its greatest axis, the greatest axis perpendicular to the midpoint of this axis being 2.0 mm. Its rostro-caudal extent was approximately 2.0 mm. Its shape in transverse sections was that of an oval, with a long axis oriented at 45 degrees with the horizontal. Its center was in the thalamus 4.8 mm. from the midline. A thin wall of glial or connective tissue sharply circumscribed the lesion, the interior of which was an almost solid mass of compound granular cells, tremendously engorged and colored deep purple by the Nissl stain. Vessels, some of them large and thick-walled, others capillary in structure, penetrated the lesion to its center, and near the periphery, the compound granular cells massed most thickly about the larger vessels. In the central part, and to a lesser extent elsewhere, were masses of closely packed erythrocytes as if in lakes, without visible endothelial limitation.

![Fig. 2. Transverse section through the caudal part of the thalamus in J610. The lesion measured 3.5 mm. in greatest axis.](image)

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No neurons or reactive glia cells were visible in the lesion. There were scattered contingents of glial nuclei along the internal wall of the capsule of the lesion. In one or two places nuclei resembling those of lymphocytes were collected. Fine amorphous granules were distributed at rare intervals along the internal aspect of the wall. Outside the wall was a very moderate gliosis. Neurons in the surrounding thalamic tissue appeared normal, although here and there an increased number of microglial or oligodendrogial nuclei was observed. There was no evidence of hemorrhage or softening in this surrounding tissue.

The lesion extended caudally to the level of exit of the third nerve.

In summary, the lesion was centered on the centromedian nucleus of the left thalamus, was roughly the shape and size of a grain of polished rice, had a thin glial and connective tissue wall, and was composed of masses of engorged compound granular cells, lakes of normal blood, and an intact vascular network. The surrounding neural tissue was apparently normal.

Sections through regions of surgical excision on left and right, indicated that the lesion did not involve the precentral gyrus, but extended caudally to include cortical tissue behind the postcentral gyrus. Some normal post-central cortex remained along the depths of sulci. Betz cells were identified in the precentral gyrus on each side though on the left side some Betz cell tissue was destroyed.

Blocks through region of cortical softening on the right disclosed changes of a chronic...
vascular inadequacy, with gliosis, absence of neurons and collections of fat-laden compound granular cells in the overlying pia-arachnoidal tissue.

In the internal segment of the globus pallidus on the left, a few neurons were pyknotic. There was a moderate increase in glial nuclei throughout, compared with the same structure on the right, which was normal. In the lateral nuclear group of the thalamus bilaterally there was a general diminution in the concentration of neurons, and a moderate gliosis, much more marked on the left.

COMMENTS

Regarding the use of aluminum salts in experimental neural lesions, Scherp and Church (4) demonstrated that convulsions, opisthotonos and nystagmus, indicating neural dysfunction, followed intracerebral injections of salts of aluminum in mice, rabbits and monkeys. Up to 37 per cent of the aluminum injected was retained in the central nervous system, and of this amount as much as 70 per cent was to be found in the cerebral hemispheres. Pharmacologic evaluations of the action of aluminum salts on normal or pathologic neural tissue have been few, and the subject deserves further study.

Kopeloff, Kopeloff and Pacella (5) detailed their method for the experimental production of epileptoid attacks by the application to the motor cortex of primates of alumina cream held in a fiber cup. The pathologic changes were those of a “chronic, proliferative meningocortical cicatrix”, which did not differ histologically from those in control cases (asymptomatic) in which the fiber cup alone had been employed, and the authors believed that the epileptogenic foci they observed indicated “an actual physiologic zone of hyperexcitability”, probably associated with the effects of the alumina cream.

There can be little doubt that the symptom pattern in the rhesus here reported, with paroxysms of starting, biting, squawling, and irritability, was that of sudden, unpleasant, probably painful paresthesia.

The parietal lesion noted at the time of the first cortical excision may have been a sole or contributing cause for the symptoms but no instances of similar experimental lesions, however, are known to have ever produced them. The thalamic lesion was placed approximately three weeks before the onset of symptoms. Kopeloff, Kopeloff and Pacella (5) observed that symptoms succeeded their lesions after a latent period of from 3 to 9 weeks. This fact, and the similarity of the painful paresthesias to those of human cases with thalamic lesions supports the conclusion that the thalamic lesions was indeed the etiologic factor for this monkey’s symptoms.

Since an extensive study of experimental paresthesia is not contemplated, this case is published for the information of those who are engaged in or wish to pursue such an investigation.

The rhesus here reported was subjected to bilateral postcentral cortical excision in two stages to evaluate effects of these removals upon the symptoms of pain of “central” origin. This has already been attempted (e.g. Horrax (6) with apparent success in the human. There is no doubt that the symptoms were alleviated. The procedure produced a mild right hemiparesis, probably a reflection of surgical impairment in function of the precentral gyrus. It did
not completely banish the symptoms, and an assessment of diminution in touch, pain and temperature perception is difficult in the rhesus. The occurrence of hypotonus contralateral to postcentral cortical excision (e.g., Peele (7)) was confirmed.

SUMMARY

1. Bilateral, apparently painful paresthesias lasting 14 weeks were observed in a rhesus monkey following a small lesion containing alumina cream, centered on the centromedian thalamic nucleus of one side.

2. After bilateral excision of cerebral cortex posterior to the central sulci the symptoms were somewhat alleviated during the final 4 weeks of observation.

3. Excision of parietal cortex unilaterally produced contralateral hypotonus.

BIBLIOGRAPHY