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Experimental Evidence on the Cerebral Origin of Muscle Spasticity in Acute Poliomyelitis.*

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One of the common symptoms of acute poliomyelitis in man and in experimental primates is the muscular rigidity, associated with hyper-reflexia, which often precedes flaccid paralysis. The considerable recent interest in this phenomenon has been associated with conflicting views as to its pathogenesis, its possible role in producing chronic deformities, and its appropriate treatment. Recent observations specifically directed at determining the characteristics and distribution of muscle spasticity in acute human poliomyelitis are in agreement with respect to the following points: 1. Muscle spasticity in acute poliomyelitis is a reflex phenomenon associated with increased stretch reflexes.[1,8] 2. Spasticity in acute poliomyelitis has a widespread occurrence in the skeletal musculature, may be present in both flexors and extensors, and may occur in partly weakened muscles as well as in muscles of normal strength.[1,2,4,6] Our observations in the rhesus monkey are in agreement with these findings in human subjects, although in some monkeys spasticity is not observed. This may result because of absence of the causes of this symptom, because of failure of detection, or because severe motoneuron paralysis occurs so quickly as to shorten greatly the period of spasticity or to preclude its occurrence. In some monkeys preparalytic spasticity may be so severe that awkwardness of gait and posture is apparent, and the resistance of extremities to passive movement is claspknife in character. At this stage a fine tremor may be present.

The fact that the lesions of paralytic poliomyelitis occur in a number of nervous centers concerned with muscle function in the brain as well as in the spinal cord, makes possible a variety of hypotheses regarding the pathological site of origin of this symptom. Added to the difficulty of analysis imposed by the widespread nature of lesions usually present in fatal human cases, is the fact that the symptom in question has usually disappeared by the time death occurs. In spite of these difficulties, it is most commonly assumed that the lesions which are responsible for the symptom of spasticity are those in the region of the spinal cord which supplies the local reflex mechanism.[3,6,8,9] Others attribute the hyperirritability of the stretch reflex to possible irritation of the muscle, nerve, posterior roots, or meninges by the virus,[4] or to lesions of sensory neurons in the posterior horns as well as in sensory ganglia.[7] None of our observations on pathological changes in many human or monkey specimens has suggested to us that lesions in these locations are quantitatively sufficient to be of primary importance in producing

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[1] Schwartz, R. P., and Bouman, H. D., *J. A. M. A.*, 1942, **119**, 923.

[2] Bouman, H. D., and Schwartz, R. P., *N. Y. State J. Med.*, 1944, **44**, 147.

[3] Schwartz, R. P., Bouman, H. D., and Smith, W. K., *J. A. M. A.*, 1944, **126**, 695.

[4] Watkins, A. L., Brazier, M. A. B., and Schwab, R. S., *J. A. M. A.*, 1943, **123**, 188.

[5] Brazier, M. A. B., Watkins, A. L., and Schwab, R. S., *New England J. Med.*, 1944, **230**, 185.

[6] Moldaver, J., *J. A. M. A.*, 1943, **123**, 74.

[7] Moldaver, J., *J. Bone and Joint Surg.*, 1944, **26**, 103.

[8] Kabat, H., and Knapp, M. E., *J. A. M. A.*, 1943, **122**, 989.

[9] Kabat, H., and Knapp, M. E., *J. Pediat.*, 1944, **24**, 123.

the generalized spasticity so common in acute poliomyelitis. It is finally obvious that the presence of lesions in the motor cortex and in brain stem centers which function to modify muscle activity, has occasionally suggested that these lesions are sources of interference with inhibitory motor mechanisms.

The difficulties of analysis of the pathogenesis of spasticity in humans can be partly overcome in rhesus monkeys because of a fortunate circumstance. We have shown that in rhesus monkeys inoculated intranasally or intracerebrally, the progress down the brain stem of lesions produced by virus activity may occasionally be arrested spontaneously at any point before reaching the spinal cord.[10,11] Such non-paralytic attacks of poliomyelitis in rhesus monkeys are not accompanied, in our experience, by severe spastic phenomena, but as a rule the lesions in the brains of such animals are not severe. However, brain lesions *may* be very severe in some inoculated animals in the preparalytic period, when spasticity is the predominant neurological symptom. It was thought possible that in some animals in this stage, virus activity or lesions might not have progressed as far as the spinal cord. With severe infections induced by most of the virus samples we have used, this is rarely true, since lesions are usually found to be present in both the lumbar and the cervical cord by the time that spasticity is well-marked.† With the Lansing strain,[12] however, we have found that not only do the arms usually show paralysis first but, in addition, the onset of paralysis in the legs is often somewhat delayed as compared with other strains.‡ Consequently, an attempt was made to kill certain animals inoculated intracerebrally with Lansing virus in the preparalytic period after definite spasticity had become manifest. It was found in 2 cases that marked spasticity and hyperreflexia were present in arms and legs *before* lesions or virus (in one case) could be demonstrated in the lumbo-sacral cord, although lesions and virus activity were present in the brain and cervical cord. An additional animal which had been inoculated with the Rockefeller MV strain in 1939 and had been killed in the preparalytic period for another purpose was subsequently found to show a similar pathological picture. It was thus apparent that lesions in the brain alone could produce the spasticity of acute poliomyelitis.

The protocols of these animals are of sufficient importance to be presented here:

Rhesus B474. This was an adolescent rhesus monkey in good condition.

Nov. 7, 1945. Under nembutal anaesthesia a trephine hole was prepared over the central sulcus in the midline, and 0.4 cc of a 10% rhesus spinal cord suspension containing the Lansing strain of virus was inoculated into each dorsal thalamus.

Nov. 12. No abnormal signs were noted.

Nov. 13. The animal was observed to be very awkward and stiff in climbing and running. Extensors and flexors of arms and legs were tense and abnormally resistant to passive movement. Deep reflexes of arms and legs were hyperactive. Head tremor was present. No weakness or difference in strength between opposite limbs could be detected by careful examination.

[10] Bodian, D., and Howe, H. A., *Bull. Johns Hopkins Hosp.*, 1941, **69**, 135.

[11] Bodian, D., and Howe, H. A., *Bull. Johns Hopkins Hosp.*, 1945, **76**, 1.

† Six rhesus monkeys killed while showing generalized spasticity in the preparalytic period after inoculation with one of 3 virus strains recently isolated from humans (Sudeck, 1941; Riley, 1943; Frederick, 1945) were found to have poliomyelitic lesions in both cervical and lumbar cord segments.

[12] Armstrong, C., *Pub. Health Rep.*, 1939, **54**, 2302.

‡ This curious strain characteristic can be illustrated by the fact that 61 of the last 81 rhesus monkeys inoculated intrathalamically with Lansing virus in this laboratory were first paralyzed in one or both arms, whereas only 6 were first paralyzed in one or both legs, and the remaining 14 exhibited both arm and leg weakness on the first day of paralysis. In contrast, only 17 of 82 monkeys inoculated similarly with one of 6 other strains isolated in this laboratory were first paralyzed in one or both arms, 20 were first paralyzed in one or both legs, and 45 had both arm and leg weakness on the first day of paralysis.

TABLE I.
Comparison of Numbers of Normal and Pathological Motoneurons in Cervical Enlargement of Rhesus B474, Based on Counts of Lateral Columns of 45 Equally Spaced 15 μ Sections (Preparalytic Poliomyelitis).

	Left	Right	Expected on basis of studies of normal controls
Normal	400	314	450-500
Chromatolytic	44	93	—
Necrotic	9	16	—
Estimated deficit§	0-47	27-77	—
Total	453-500	450-500	450-500

§ Motoneurons absent because of complete autolysis or phagocytosis.

Under ether anaesthesia, the animal was perfused through the aorta with 10% formalin containing 1% acetic acid. The brain and spinal cord were removed for histological study. Serial sections at 15 μ were prepared of the cervical cord from C6 to T1 inclusive, and of the lumbosacral cord from L2 to S1 inclusive. All sections of the above 8 lumbosacral segments were stained with gallocyanin and examined.

Histopathological Findings. Sections of the cervical cord contained typical early lesions of poliomyelitis, with moderate perivascular and diffuse leucocytic infiltration, and neuronal changes. Relatively few neurons were destroyed, but a considerable number showed various degrees of chromatolysis. The left anterior horn was almost free of lesions except in the lower part of C8 and the upper part of T1. Actual motoneuron destruction on the right side was limited to segment C7, although various degrees of chromatolysis were present in all cervical segments. An actual count of the anterior horn cells in 45 sections taken at intervals through the cervical enlargement showed the distribution of normal and affected motoneurons seen in Table I.

A quantitative study of the relationship of motoneuron destruction to muscle weakness, now in progress, indicates that the amount of motoneuron damage in the cervical cord was far below the level which produces clinically evident weakness.

All sections of the lumbosacral enlargement (L2 to L7, and S1) were examined. No lesions of poliomyelitis were detected.

The brain was imbedded in celloidin and sectioned at 60 μ. Every 20th section was stained with gallocyanin and examined. A typical distribution of severe focal and diffuse infiltrative lesions and of neuronal destruction was found. Severest lesions were observed in the motor cortex (areas 4 and 6 of Brodmann), dorsal thalamus, fields of Forel, substantia nigra, superior colliculi, midbrain tegmentum, reticular formation of hindbrain, vestibular nuclei, and basal cerebellar nuclei. Neuron destruction, however, was most marked in the reticular formation and in the large cells of the vestibular nuclei.

Rhesus 959. This was an adolescent female, slender but active.

March 17, 1939. Under ether anaesthesia a trephine hole was prepared over the right motor cortex and 0.2 cc of a 20% rhesus cord suspension containing the Rockefeller Institute MV strain of virus was injected in the cortex of the leg region.

March 23. Rectal temperature had risen from a base-line of 102°F. on March 21 to 105.2°F. No muscular weakness was detected by observation of movements or by palpation. The right leg, however, was observed to be definitely more spastic than the left leg or arms, and the right knee jerk was more active than the left. Under ether anaesthesia, the animal was perfused through the aorta with 10% formalin containing 1% acetic acid. The brain and spinal cord were removed for histological study. Serial celloidin sections at 30 and 60 μ were prepared of the brain, and paraffin sections at 15 μ of the cervical and lumbar cord, and these were stained with gallocyanin.

Histopathological Findings. Typical inflammatory lesions were found at all levels of the cervical cord examined from C6 to T1. These lesions were very light, however,

TABLE II.‖
Subinoculation Tests of Suspensions of Anterior Quadrants of Spinal Cord Enlargements of Rhesus B430 (Preparalytic Poliomyelitis).

		Deaths or paralyses among inoculated animals			
	Virus Dilution	Rt. Cervical	Lt. Cervical	Rt. Lumbar	Lt. Lumbar
Mouse Tests	10^{-1}	11/16	7/8	0/8	0/8
	$10^{-1.5}$ and 10^{-2}	8/16	12/16	0/8	0/8
	$10^{-2.5}$ and 10^{-3}	4/14	4/14	0/8	0/8
	10^{-4}	1/16	1/16	0/8	0/8
Monkey Tests	10^{-1}			0/1	0/1

‖ The mouse titrations were part of a larger study of virus levels in infected monkeys being carried out in collaboration with Dr. Mary Cumberland. In this study it was found that intracerebral inoculation in rhesus monkeys was a more sensitive test for the presence of Lansing virus in monkey cord than was mouse inoculation. The monkeys shown in this table were inoculated intrathalamically and killed after three weeks. Sections of cord and brain were examined and found normal. Not enough material was available for additional monkey tests.

and sparse at C8 and T1. Neuronal changes were found only on the right side in segment C7. These consisted mostly of various degrees of chromatolysis with only about 4% of all cells on the left side destroyed.

Complete serial sections of the lumbar cord segments L3 to L7, and S1, were stained and examined. No lesions of poliomyelitis were found.

Every 20th section of the brain was stained and examined. A typical poliomyelitic distribution of moderate to severe perivascular and focal infiltrative lesions and of neuronal destruction was found. A predominance of severe lesions was observed on the right side of the brain stem, especially in globus pallidus, subthalamic centers, midbrain tegmentum, reticular formation, and vestibular nuclei. Lesions were not observed in the left cerebral cortex or thalamus.

Summary of Rhesus 959. This animal was of interest in that the only preparalytic symptoms noted were fever, and spasticity and increased knee tendon reflex of the right leg. Lesions were absent in the lumbar cord, and in the left motor cortex, but were severe on the right side of the brain stem, especially in the globus pallidus, subthalamic centers, midbrain tegmentum, reticular formation, and vestibular nuclei. If cortical involvement had been responsible for spasticity of the right leg, lesions would have been expected on the left side, but none were found there. The right-sided unilaterality of spasticity in this case is suggestively associated with ipsilateral predominance of lesions in the brain stem.

Rhesus B430. This was an adolescent animal in good condition.

Aug. 30, 1945. Under nembutal anaesthesia a trephine hole was prepared over the central sulcus in the midline, and 0.4 cc of a 5% rhesus cord suspension containing the Lansing strain of virus was inoculated into each dorsal thalamus.

Sept. 4. Rectal temperature had risen to 105°F. from a baseline of about 104°.

Sept. 5. The animal now was very awkward and stiff in running and climbing, and had marked head tremor. Palpation revealed that arms and legs were very strong, but very resistant to passive manipulation. All muscle groups appeared to be tense, but especially the forearm flexors and the hamstring muscles showed rigidity of the clasp-knife type. Tendon reflexes were exaggerated.

Under ether anaesthesia, the animal was exsanguinated from the femoral arteries. With sterile precautions, the cervical and lumbar enlargements of the spinal cord were removed separately for virus assay. The animal was then perfused through the aorta with 10% formalin containing 1% acetic acid. The brain and remainder of the spinal cord were removed for histological study.

Results of Virus Assays. Right and left anterior quadrants of cervical and lumbar enlargements were prepared separately as 10% aqueous suspensions. Subinoculations were done in mice and in rhesus monkeys, with

the results seen in Table II.

Histopathological Findings. Segments of cord above and below the cervical block removed for virus, of various thoracic levels, and of the upper lumbar cord were imbedded in paraffin, sectioned serially at 15 μ, stained with gallocyanin, and examined. Cord from C1 to C3 contained numerous lesions of poliomyelitis, including perivascular and diffuse leucocytic infiltration, and chromatolysis and phagocytosis of nerve cells. Sections of cord at T2, T3, T5, T9, T11, T12, L1, and L2 were quite free of any lesions of poliomyelitis.

The brain was imbedded in celloidin and sectioned at 60 μ. Every 20th section was stained with gallocyanin and examined. A typical distribution of severe focal and diffuse infiltrative lesions and of neuronal destruction was found. Neuronal destruction and inflammatory changes were particularly severe in the reticular formation, especially in the pons region, and in the vestibular nuclei. Severe changes were also present in the midbrain tegmentum, in the fields of Forel, and in the substantia nigra. Lesions in the above-mentioned centers were roughly equal on both sides, but in the forebrain there was a predominance of lesions of moderate intensity in the left dorsal thalamus and in the left pre- and postcentral cortex. Lesions in the right thalamus and cortex were very few in number, and in fact absent in most sections examined.

Summary of Experiment B430. The failure to obtain virus from the lumbar enlargement or to find lesions in the thoracic or upper lumbar cord, whereas both lesions and virus were present in the cervical cord, is sufficient evidence that virus activity had not yet reached the lumbar cord in this animal.

Discussion. The evidence cited in this report indicates that neither virus activity nor lesions in the spinal cord are necessary pathogenetic factors for the production of spasticity in acute poliomyelitis. The marked spasticity seen in the legs of the monkeys described, in the absence of pathological changes in the lumbosacral cord, must be attributed to the pathological changes present in the brain or cervical region of the spinal cord. Although the lesions in the cervical cord could have affected the long propriospinal neurons connecting with motoneurons in the lumbar cord, this is doubtful since the lesions in the cervical region were quantitatively very mild. Severest damage in the brain in primate poliomyelitis including the greatest amount of nerve cell destruction most often occurs in the reticular formation of the hindbrain and in the vestibular centers. These centers are connected with motoneurons of the spinal cord either directly or by way of internuncial neurons, as is well known.[13] Magoun has made the interesting observation that stimulation of the bulbar reticular formation can have a generalized inhibiting effect on motor activity induced reflexly or by brain stem or cortical mechanisms,[14] and Wagley[15] has recently introduced evidence for the production of spasticity in rhesus monkeys by reticulospinal tract section.¶ These findings suggest that it is the severe lesions in the reticular formation in acute poliomyelitis which may be at least in part responsible for generalized spasticity, because of destruction of many "inhibitory" neurons. It is also of interest that all of the animals described in this account had almost fully developed pathological changes in the brain before limb paralysis was manifest.

[13] Lloyd, D. P. C., *J. Neurophysiol.*, 1941, **4**, 115.

[14] Magoun, H. W., *Science*, 1944, **100**, 549.

[15] Wagley, P. F., *Bull. Johns Hopkins Hosp.*, 1945, **77**, 218.

¶ The cells of origin of this tract are the large neurons scattered in the central part of the reticular formation from the level of the superior colliculus caudalward.[16] In a rhesus monkey prepared by Dr. Howard A. Howe and surviving 8 days after hemisection of the spinal cord at the first cervical segment, I found extensive and severe chromatolysis in these cells. The chromatolysis was bilateral but predominantly ipsilateral. It was estimated from counts made of every twentieth section of a 30 μ series, that the number of reticulospinal neurons on each side was of the order of one thousand. It is likely that these cells are part of a chain of neurons which form at least part of the extrapyramidal pathways from motor cortex to spinal cord (see review of Hines[17]).

[16] Papez, J. W., *J. Comp. Neur.*, 1926, **41**, 365.

[17] Hines, M., *Biol. Rev.*, 1943, **18**, 1.

The fact that spasticity can be produced without lesions being present in the spinal cord does not preclude the possibility, suggested by Kabat and Knapp,[8,9] that lesions in the internuncial neurons of the spinal cord can produce a similar effect under certain circumstances. As Lloyd[13] emphasizes, certain internuncial neurons in the cord are an integral part of the mechanism of reticulospinal and propriospinal action on the motoneurons. Kabat and Knapp have introduced as evidence in this connection the inconclusive observation that most spinal cords from fatal human cases have lesions in the intermediate columns where the internuncial neurons presumably are predominantly present, and that some cases have internuncial lesions with "relatively normal anterior horn cells." Unless serial sections of several segments at the involved level are examined, which was not implied, such a statement is necessarily inaccurate since lesions in the spinal cord may be quite spotty in character. For example, sections separated by only a millimeter or less may show quite different degrees of involvement of anterior, intermediate, or posterior cell columns.[10] It is therefore obvious that only a quantitative study of the degree of neuron destruction in the spinal cord centers at various levels, based on a detailed study of serial sections, and correlated with symptoms referable to affected levels in each case, can yield anything more than suggestive inferences in a problem of this kind. On the other hand, the evidence from preparalytic animals, as we have noted before,[18] can at times give a clear-cut answer on problems of pathogenesis because in such animals the pathological picture is in process of development and much less difficult of interpretation than that in fatal cases. The absence of lesions or detectable virus activity in the lumbosacral cord in the preparalytic period of animals already showing spasticity of leg muscles, is an unusually good example of this.

Summary. Evidence is presented which demonstrates that neither virus activity nor lesions in the spinal cord are necessary pathogenetic factors for the production of the spasticity of acute poliomyelitis. In 2 rhesus monkeys inoculated intracerebrally with poliomyelitis virus and killed in the preparalytic period when marked spasticity was present in the muscles of the legs, as well as elsewhere, no lesions were present in complete serial sections of the lumbosacral cord. In an additional similar case it was also found that no virus was present in the lumbosacral cord. In all cases severe lesions were already present in most of the brain centers usually involved, and neuronal destruction was especially severe in the midbrain tegmentum, reticular formation of the hindbrain, and in the vestibular nuclei. It is concluded that lesions in the brain alone can produce the spasticity of acute poliomyelitis. The pathological origin of this symptom is discussed, and evidence cited for the possible causative role of lesions in brain stem centers, especially the reticular formation.*

[18] Bodian, D., and Howe, H. A., *Brain*, 1940, **63**, 135.

* While this paper was in press, Dr. Isabel Morgan reminded the author that Bodian and Howe[18] in 1940 (p. 152) described two relevant rhesus monkeys killed in the preparalytic stage following intrasciatic virus inoculation. When killed these animals had generalized prodromal muscle tenseness, although lesions had not progressed rostrally beyond the midbrain tegmentum in one case or the hypothalamus in the other, so that no cortical lesions were found. A resurvey of serial sections of the central nervous system of both of these cases showed that lesions were absent in vestibular nuclei, very light in the cervical cord, and very severe in the reticular formation of the pons region.