# EXPERIMENTAL EPILEPSY IN THE MONKEY FOLLOWING MULTIPLE INTRACEREBRAL INJECTIONS OF ALUMINA CREAM*

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THE multiple intracerebral injection of alumina cream (aluminum hydroxide cream) into a principal cerebral sensorimotor cortical area is effective in producing chronic epilepsy in monkeys.[1] Some of the clinical, pathological and electroencephalographic features of such epileptic animals, supplemented by a motion picture demonstration of a reactive monkey, are the subject of the present report.

*Method*: Alumina cream was injected into eight areas of the exposed sensorimotor cortex of one cerebral hemisphere (Fig. 1) in six Macaca mulatta and into both cerebral hemispheres in an additional monkey. Injections of 0.1 ml. alumina cream were made slowly through a 26 gauge hypodermic needle inserted almost perpendicularly to a depth of 3 to 11 mm. The estimated amount of alumina cream retained in each cerebral hemisphere following injection varied from 0.3 to 0.6 ml. Animals were observed following operation for periods up to nine and one-half months, during which time serial electroencephalograms (EEG), clinical observations and motion picture studies were made. Brains were studied postmortem and the injection sites plotted.

*Results*: In all injected animals a variable degree of contralateral hemiparesis was obvious immediately after operation. In five of the six monkeys injected unilaterally, spontaneous contralateral focal motor seizures were evident three to four weeks after operation. Initially there occurred almost continuous twitch-like movements of varying amplitude and regularity, involving the musculature of the contralateral face and limbs. Excitement, agitation, movement or stress readily aggravated and accentuated this type of motor activity and sometimes led

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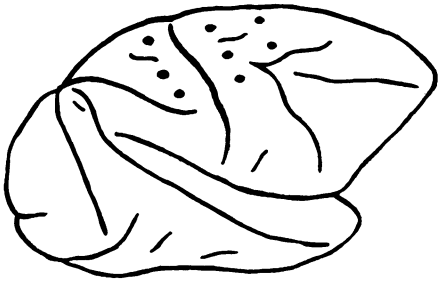

***Figure 1.*** **Diagram of lateral aspect of cerebral hemisphere of Macaca mulatta with sites of injection indicated by heavy dots.**

to Jacksonian spread with full-blown generalized convulsive seizure and exhaustion. During the following few weeks, spontaneously occurring Jacksonian motor seizures with spread became a more prominent feature. The twitch-like muscle movements then became less evident, the animals continuing to exhibit spontaneous Jacksonian seizures and marked susceptibility to motor seizures by prodding or stress. These animals thereafter resembled in their epileptic behavior other monkeys made epileptic by application of a disc containing alumina cream to one sensorimotor cortex.[2] The monkey in which multiple injections were made into both cerebral hemispheres expired in generalized status epilepticus two weeks after the onset of seizures and five weeks after operation despite treatment with large doses of parenteral phenobarbital.

Postmortem examination of the brains disclosed a meningocerebral cicatrix extending over the zone of cerebral injections with scarring of the underlying cortex and subcortical white matter. The sites and needle tracks of alumina cream injections were in general grossly visible in coronal sections. Microscopic examination revealed that the needle tracks contained masses of more or less homogenous injection mass with collections of gitter cells most prominent near the borders. The reaction of the brain tissue around the deposits of alumina cream was variable and in some areas a minimal pathological reaction was seen. Vascular zones containing many vessels with thickened endothelial layers projected from some edges of the needle tracks (Fig. 2). Cerebral tissue adjacent to the tracks frequently showed evidence of severe neuronal changes, intense astrocytic gliosis, markedly increased vascularity and demyelinization of subcortical white matter. The deep-

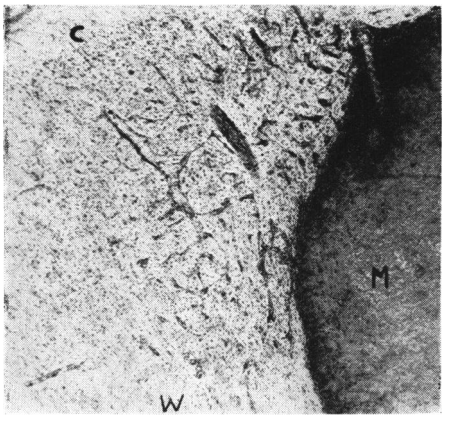


*Figure 2.* Cerebral area bordering injection mass (M) with reactive vascular zone extending into cortex (C) and adjacent white matter (W). (H & E x 68). Monkey #653.

est injections (11 mm.) were made in the only monkey which did not exhibit spontaneous seizures, and extended into the superior putamen and internal capsule. Occasional small cyst formation was evident at some injection sites.

Following multiple intracerebral injections of alumina cream pronounced changes occurred in the electroencephalogram (Fig. 3). During the initial, relatively continuous convulsive phase, high amplitude (300-400 $\mu$v) serial spike, or spike and slow wave formations were most pronounced over the injected cerebral site. In the following stage this type of abnormality gradually became less evident, the tracings showing an increased amount of mildly slowed frequencies of increased amplitude. The rapid intravenous injection of 0.1 to 0.15 ml. 10 per cent Metrazol at this time usually promptly provoked focal random or serial high amplitude spike discharges, and was sometimes accompanied by motor convulsive manifestations. In electrocorticograms made from exposed brain and scarred area (Nembutal anesthesia) runs of serial spikes and random spike activity were present simultaneously in widely separated areas. In the monkey with the shallowest injections (3 mm.) the EEG was unusual in that recurrent spindle bursts of fast activity (18-22/sec.) occurred over the injected site (Fig. 4). Apparent transmission of spike, or spike and slow wave activity to homologous areas of the non-

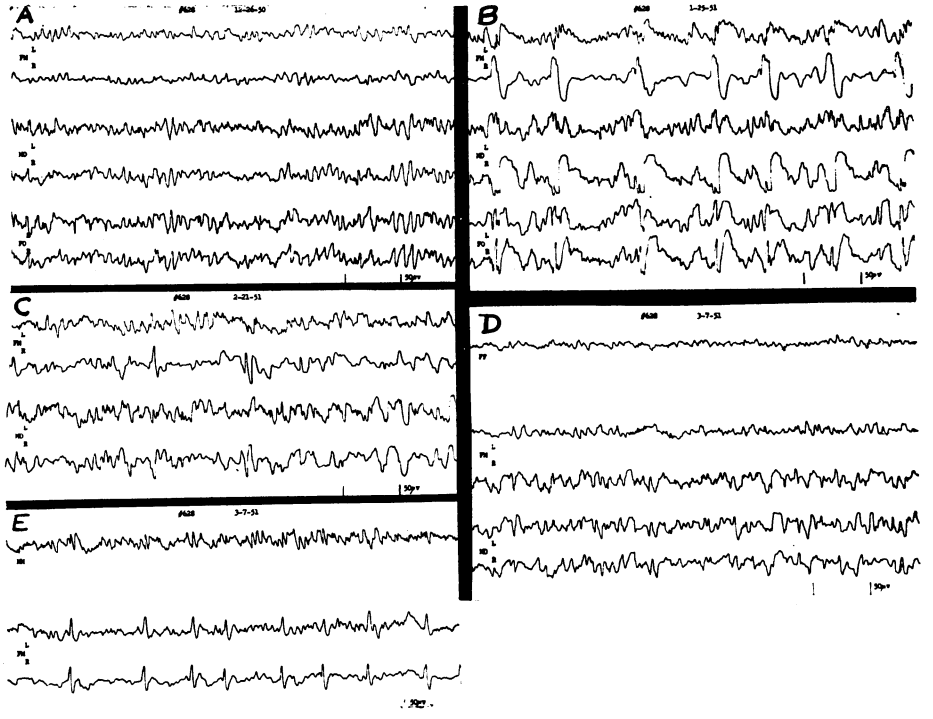


*Figure 3.* Serial electroencephalograms of monkey #628 following multiple intracerebral injections of alumina cream.

A 12/26/50 Control preoperative tracing.
B 1/25/51 4 weeks after injection.
C 2/21/51 8 weeks after injection.
D 3/7/51 10 weeks after injection.
E 3/7/51 10 weeks after injection following intravenous Metrazol (10 mg.).

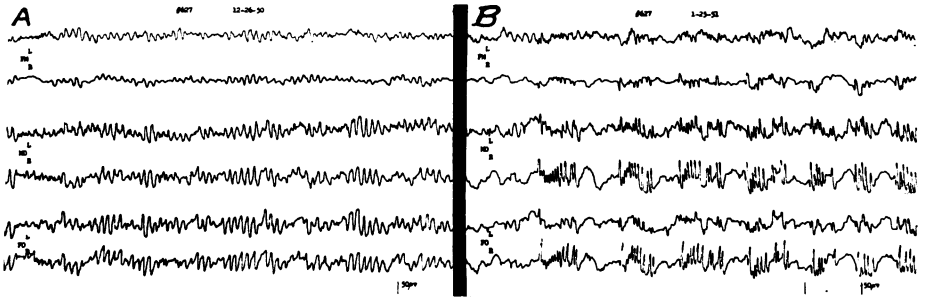


*Figure 4.* Electroencephalograms in monkey #627 with shallow injections.

A 12/26/50 Control preoperative tracing.
B 1/25/51 4 weeks after injection.

injected cerebral hemisphere commonly occurred, with these patterns most evident in the first weeks following onset of motor convulsive activity.

## Discussion

The focal motor epileptic manifestations present at the onset of epilepsy in the monkeys following multiple intracerebral sensorimotor injections of aluminum hydroxide cream so closely resembled human epilepsia partialis continua that they would appear to be the simian counterpart. The form of human motor epilepsy known as epilepsia partialis continua was first reported by Koshewnikow.*[3] Wilson[4] described epilepsia partialis continua as "Another motor variant, doubtless somewhat rare, differs from the general myoclonic type in that the twitching is limited to one segment of the body (hence the term 'mono-epilepsy') nearly always peripheral, such as wrist and fingers, is virtually continuous between infrequent paroxysmal Jacksonian generalized fits, and on the whole consists less in formed movements than in irregular muscular contractions. Known also as 'polyclonia epileptoides continua', most though not all of the reported cases have had a background of structural disease of the cortex." Penfield and Erickson[5] stated that epilepsia partialis continua "may be defined as a local convulsive movement of one part of the body which continues steadily, or with brief interruptions, over long periods of time. It may be a localized continuing myoclonic seizure, or it may be a simple focal motor seizure in which discharge does not spread across the cerebral cortex but remains limited." Radermecker and van Bogaert[6] among others, have emphasized that "Kojewnikoff epilepsy" clinically resembles excitation or liberation of the cortex and noted that there exists a whole range of transitions between the unilateral clonic movements in some cases of "ordinary" epilepsy and epilepsia partialis continua.

Since the injections of alumina cream were made intra- and subcortically the essential clinical and pathophysiological changes are believed to have resulted from local cortical and superficial subcortical white matter changes. Motor function for the principal cerebral sensory as well as for the motor area has been well established in the monkey[7, 8] so that in these injected animals a wide area of cortical and subcortical chronic motor facilitation and stimulation was probably

* Also referred to as Kojewnikoff, Koschewnikoff, Koschewnikow or Kojewnikov.

achieved. A similar clinical reaction occurred in a previously unreported monkey with multiple intracerebral injections of alumina cream confined to a precentral motor zone (Area FA, FB, FBA); a like result was obtained with multiple injections of alumina cream confined to a post-central gyrus (Area PE, PEm). It should be noted in this connection that Töbel and Schaltenbrand[9] reported a human case of "Kojewnikoff syndrome" associated with a small abscess located in the white matter of a parietal lobe near the junction of cortex and subcortical white matter.

We do not know why motor epilepsia partialis continua rather than ordinary Jacksonian convulsions or seizures with Jacksonian spread occurred in the early stages of the epileptic reaction. One may speculate that spread of impulses from any single site to produce a Jacksonian seizure may have been hindered by a local relative refractory state following the more or less constant asynchronous excitation of the various cortical zones injected. Intracortical spread of excitation may have been more difficult at this stage because the stimulant effect was produced in deeper cortical zones and in subcortex distal to the superficial layers of cerebral cortex. The possibility also exists that the threshold for motor excitation of deeper, efferent cortical cells and fibers of the sensorimotor cortex was considerably less than that of other routes of transmission. Irregular stimulation of small aggregates of motor efferent cells of insufficient magnitude to reach a critical value or form necessary for Jacksonian spread might also have been a factor. Furthermore, the injection treatment may have shortcircuited intracortical relays so that involvement and participation of full-thickness cortical neuronal chains occurred rarely or only under the facilitating effect of agitation, stress, movement or excitement.

During the early epileptic phase, the electroencephalograms contained more or less continuous high amplitude spike, or spike and slow wave discharges, most intense over the cerebral site that had been injected. These patterns persisted during phases of intense epilepsia partialis continua, becoming less prominent thereafter. When relatively small muscle segments were involved in twitching or myoclonic responses, a direct correlation between components of the electroencephalogram and visible abnormal muscle motor activity could not be established. Occasionally, for short periods of time, especially when more massive focal myoclonic responses occurred, spike discharges in the EEG seemed

to occur synchronously with visible abnormal motor activity. During the ensuing stages, spike activity was generally replaced by high amplitude serial slow wave activity. Intravenous Metrazol (0.1 to 0.15 ml. 10 per cent solution) promptly evoked spike, or spike and wave discharges from the injection sites and frequently also from the homologous contralateral cerebral area. Although such responses might occur without visible motor reaction, at times they were associated with or soon followed by a focal myoclonic, Jacksonian or generalized motor seizure. Spindle bursts of fast activity such as occurred in the monkey with shallow intracerebral injections represent a highly unusual EEG pattern in epileptic monkeys and are ordinarily not associated with the epilepsy which follows application of alumina by disc to the cerebrocortical sensorimotor surface.

## Summary

1. Clinical, pathological and electroencephalographic features of monkeys made epileptic by multiple intracerebral injections of alumina cream into a principal sensorimotor area are presented.

2. The early motor convulsive manifestations in such epileptic monkeys resemble the motor form of human epilepsy described as epilepsia partialis continua (Koshewnikow).

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## *REFERENCES*

1. Chusid, J. G., Pacella, B. L., Kopeloff, L. M. and Kopeloff, N. Chronic epilepsy in the monkey following multiple intracerebral injections of alumina cream, *Proc. Soc. exp. Biol. Med. 78*:53-54, 1951.
2. Kopeloff, N., Kopeloff, L. M. and Pacella, B. L. The experimental production of epilepsy in animals, in *Epilepsy*, New York, Grune & Stratton, 1947, pp. 163-180.
3. Koshewnikow. Eine besondere Form von corticaler Epilepsie, *Neurol. Cbl. 14*:47-48, 1895.
4. Wilson, S. A. K. *Neurology*. London, Edward Arnold, 1940, v. *2*, p. 1501.
5. Penfield, W. and Erickson, T. C. *Epilepsy and cerebral localization*. Springfield, Ill., Charles C. Thomas, 1941, p. 25.
6. Radermecker, J. and van Bogaert, L. Sur l'épilepsie partielle continue (Kojewnikoff), *Mschr. Psychiat. Neurol. 118*:273-87, 1949.
7. Sugar, O., Chusid, J. G. and French, J. D. A second motor cortex in the monkey (Macaca mulatta), *J. Neuropath. exp. Neurol. 7*:182-89, 1948.
8. Woolsey, C. N., Travis, A. M., Barnard, J. W. and Ostenso, R. S. Motor representation in the postcentral gyrus after chronic ablation of precentral and supplementary motor areas (abstract), *Fed. Proc. 12*:160, 1953.
9. Töbel, F. and Schaltenbrand, G. Beitrag zur Frage der Lokalisation und Entstehung des Kojewnikoffschen Syndroms (Epilepsia partialis continua), *Nervenarzt 18*:501-05, 1947.