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EXPERIMENTAL STUDIES ON PONTINE EPILEPSY PRODUCED BY INJECTION OF ALUMINA CREAM IN CATS

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INTRODUCTION

In 1955, we experienced a patient of the probable pontine epilepsy which had already been reported by ARAKI and others (1956).

In this patient, it was almost decisive that the lesion was located in the left pontine region in view of the presence of crossed sensory and motor disturbance. And the patient, whenever the pain stimuli of sufficient intensity were given to any part of his body, used to fall down losing consciousness instantly, and meanwhile gave rise to the seizure, which represented not typical grand mal pattern but tonic contractions or intermittent twitchings.

EEG record during the seizure showed a tendency of desynchronization and no distinct spike discharge could be noted in ictal as well as pre- and postictal periods.

On the other hand, in various animal experiments in our laboratory, it was demonstrated that in case of transient coma immediately following destruction or stimulation of the brain stem, EEG generally showed low voltage fast waves for a while. Now it is particularly interesting for us that the EEGs in our case of the pontine epilepsy showed desynchronization just as we had observed in these animal experiments.

Moreover, this experience made us consider that in the maintenance of alert condition, not only the midbrain but also the pons and the medulla might play an important role likewise.

Present study has been performed to examine experimentally the peculiar features in seizure and electroencephalogram represented by the pontine epileptic patient, and the correlation between the pontine region and consciousness.

In order to produce the pontine epilepsy experimentally, alumina cream (a colloidal precipitate of ammonium hydroxide and ammonium alum, the abbreviation a. c. will be used in this report) prepared by KOPELOFF's method (1942) was injected into the one half of pons.

MATERIAL AND METHOD

1. 89 cats weighing from 3 to 4 kg were used in all.

2. Alumina cream (a. c.) was prepared by KOPELOFF's method, that is, by adding a slight excess of 1% ammonium hydroxide at room temperature to a 1% solution of ammonium alum and resting precipitate was washed by decantation until no trace of ammonium-ion was certified in the supernatant fluid.

NESSLER's reagent was used in order to detect ammonium-ion. Then using centrifuge a colloid was prepared, containing about 3 mg of Al in 1 cc.

3. Injection was carried out with an injection needle with an internal diameter of 2 mm under the guidance of HORSLEY-CLARKE's stereotaxic instrument, and a. c. from 0.05 to 0.15 cc was injected only once into the one half of pons.

4. Installation of stereotaxic instrument and outfitting of leading electrodes were performed under ether anesthesia. Following steps of the experiment were carried out usually in the state where the animal was fully awake behaviorally as well as electroencephalographically.

5. Leading electrodes for surface EEG usually consisted of silver ball electrodes, 4 or sometimes more in number.

These electrodes were inserted passing through the skull, and fixed to the level of dura. Location of 4 silver ball electrodes were as follows: (1) frontal point which is 1.5 cm rostral to the coronal suture in the median sagittal line; (2) occipital point which is 1.5 cm rostral to the external occipital protuberance in the midline; (3) left temporal point which is 2 cm left to the midline of skull; (4) symmetrical point of (3) on the right side.

6. Deep electrogram was recorded by means of two parallel arranged steel wires of 0.3 mm in diameter which were insulated except for 1 mm of the tips.

7. EEG and EMG were recorded routinely with 2 channel (SANEI) or 8 channel (EDISWAN) inkwriting oscillograph.

Exact pattern of seizure was observed cinematographically.

8. After injection of a. c., metrazol provocation had not been done even once, until the seizure occurred spontaneously.

9. In this report, disturbance of consciousness was defined as follows:

1) Semicoma (unresponsiveness 2nd degree).

The postural reflex is completely abolished. The active movements and the reflexes to smell stimuli are also gone. The reflexes to visual, acoustic and touch stimuli are absent. The reflex to pain stimuli against the body surface is attenuated but partially remains. The sneeze reflex by stimulating septum nasi, the reflex to painful stimuli of nasal tip and the vomiting reflex due to stimuli of pharyngeal mucosa remain.

2) Coma (unresponsiveness 3rd degree).

The reflex to stimuli of nasal tip and septum nasi and the vomiting reflex due to stimuli of pharyngeal mucosa are absent. The corneal reflex, the pupillary reflex, and the pinna reflex are sometimes present. Patellar reflex remains.

10. After putting the experimental animals to death, site of the a. c. injection and location of tips of deep electrodes were ascertained histochemically by means of iron-eosin stain and aluminon method (OKAMOTO 1944).

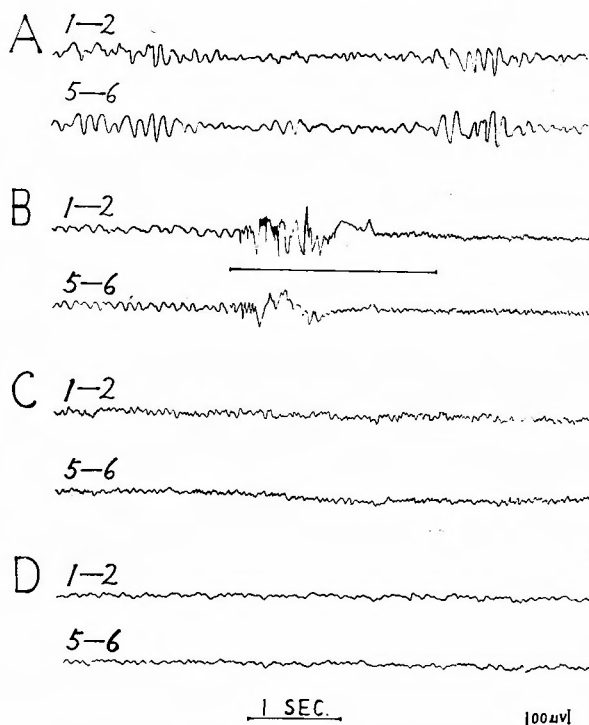
Anatomical guidance was obtained mainly from WINKLER & POTTER (1941) and JASPER & AJMONE-MARSAN (1955).

RESULTS

1) Changes of EEG and of behavior induced immediately after the injection of a. c.

In 9 cases out of 16, both in the surface EEGs and in deep electrograms recorded from the pontine region low voltage fast waves dominated as soon as a. c. was injected. And as time passed, the activities, being substituted gradually by slow waves, came to show low voltage slow waves after from several minutes to several hours (Fig. 1).

Fig. 1 Electrographic changes induced immediately after the injection of a. c.



1-2: Surface EEG.

5-6: Deep record led bipolarly from pontine reticular formation.

A: Before in Jection.

6-20 p. s. regular rhythm intermingled with high voltage spindle bursts.

B: Injection of a. c.

Line drawn between tracing 1-2 and 5-6 indicates a. c. injection.

Immediately after the injection, electrographic activities changed into low voltage fast ones (mainly 15-40 p. s. below $30 \mu V$), while animal fell into unresponsive state.

C: 50 sec. after injection.

Desynchronized electrograms and unresponsive state still continued.

D: 3 min. after injection.

Responsivenss returned but not to normal. Electrograms were transformed gradually into low voltage slow waves.

Among the other 7 cases which did not show the desynchronization, in 3 cases low voltage slow waves dominated from immediately after the injection, and in 4 cases any marked changes could hardly be observed.

These postinjectional electrographic changes used to subside in from several days to over ten days.

56 animals out of 74 (about 76%) of our experiments, fell into transient (3-10 minutes) unresponsive state immediately after the injection.

It was difficult to see distinctly the mutual relationship between electrographic changes and animals' responsiveness, but all the cases in which postinjectional EEG showed the desynchronization, fell into transient coma, and many of them brought back responsiveness about the time when slow waves dominated in electrograms.

During coma there were no accompanying twitches or convulsions (tonic or clonic).

In some cases, after recovery from coma, circling movement to the contralateral side and contralateral hemiplegia were observed temporarily, but they usually became convalescent completely within a week, and thereafter any remarkable change could be observed in neither EEG nor behavior, until the convulsive seizures without any provocation occurred.

2) Convulsive seizures induced by a. c.

Except 29 cases which seemed to have died of meningitis, brain abscess and bleeding in the 4th ventricle and so on as results of injection or implantation of electrodes, in 9 cases out of 39 (about 23%) seizures occurred late after a. c. injection into the one half of pons (Tab. 1).

Table 1

cat number	a. c. dosage (cc)	seizures		type
		initiation after injection (days)	duration (hours)	
7	0.08	45	8*	persisting myoclonic convulsions intermingled with tonic fits
11	0.08	155	48	
18	0.08	60	56	
33	0.08	265	58	
40	0.07	58	3*	
58	0.12	138	24*	
68	0.15	22	4	generalized tonic-clonic convulsions
61	0.12	22	20	
72	0.13	182	15	

* sacrificed

A. The type of convulsions

In all but 2 cases among these 9, seizures were of myoclonus pattern intermingled with tonic fits which covered almost the entire body simultaneously, and, once arisen, persisted and the animals fell in status epilepticus and died in a little while.

In the other 2 cases, recurrent tonic-clonic convulsions, that is, grand mal pattern in man (GIBBS 1943), were observed, but among these series of repetitive convulsions, some attacks did not develop into grand mal, remaining in tonic convulsions.

Seizures could be elicited readily by sensory stimulations such as stab and heat, thus the tendency of "reflex epilepsy" was noted.

B. Electroencephalogram during the seizure

Among the cases showing myoclonic convulsions, both surface EEG and deep electrograms could be recorded in 3 cases and the surface EEG only in 2 cases, and in all these cases surface EEGs showed the fast activities and any spike discharge could hardly be noted. While the deep electrogram recorded from the pontine reticular formation consisted of the spike or sharp waves associated with high voltage slow waves, and close relationship could be observed between the seizure discharge in deep record and myoclonic twitches.

Moreover, multiple-spikes-and-wave complex or sharp-and-wave complex (LENNOX 1945 and others) which are sometimes observed in myoclonic seizure of a man, were seen as well in the deep electrogram.

In two cases which represented grand mal pattern, rhythmic series of high voltage fast waves were noted both in the surface and deep records. But sometimes hypersynchronous neuronal discharges were noted only in the deep record and similar activities in cortical records used to be retarded to occur. During the period when only the deep record showed seizure discharges, the animal revealed remarkable tonic state and it was only when the animal manifested grand mal that seizure discharges were noted in the surface EEGs.

C. Changes of animals' behavior during the seizure.

As for the animals' responsiveness to nociceptive stimuli during the seizure, one case (No. 61) represented the unresponsive state to painful stimuli for several minutes (coma) at the tonic stage of grand mal pattern seizure. Two cases (No. 40, No. 58) among those showing tonic and/or myoclonic convulsions, lost the postural reflex and the reflex to touch-stimuli, but responded slightly to painful stimuli (semicoma).

In all other cases, no mew and no spontaneous movement was observable and postural reflex disappeared incompletely, but the responsiveness to painful stimuli remained almost normal, and pinna reflex was also preserved completely.

Tachypnea was observed in all cases, and rise in body temperature (No. 7, No. 40) and micturition (No. 7, No. 18, No. 61) were observed in some cases.

Animals showing tonic convulsions, generally flexed their fore- and hindlimbs at the elbow and knee, and the increase of muscle tonus was more remarkable at the

* According to the clinico-anatomical classification of epilepsy by PENFIELD and JASPER, the term "myoclonic seizure" has been dropped and "myoclonic petit mal" or "grand mal" is used instead of it. But, at present when their theory of centrencephalic system is no more than a hypothesis, we apply in this report the term "myoclonic seizure" which widely means epilepsy that shows myoclonic convulsions, as the term has long been in use. Therefore, this term has also different meaning from "myoclonus epilepsy" (UNVERRICHT 1895).

limbs opposite to injection.

(1) Case 33

0.08 cc of a. c. was injected into the middle level of the left half of pons (Fig. 2).

Fig. 2 Transverse section of the pons showing the greatest extent of the lesion in cat No. 33.



The animal fell into coma immediately after the injection, remaining so for about 3 minutes. After recovery he was stuporous for several days, but any subsequent changes could not be observed behaviorally.

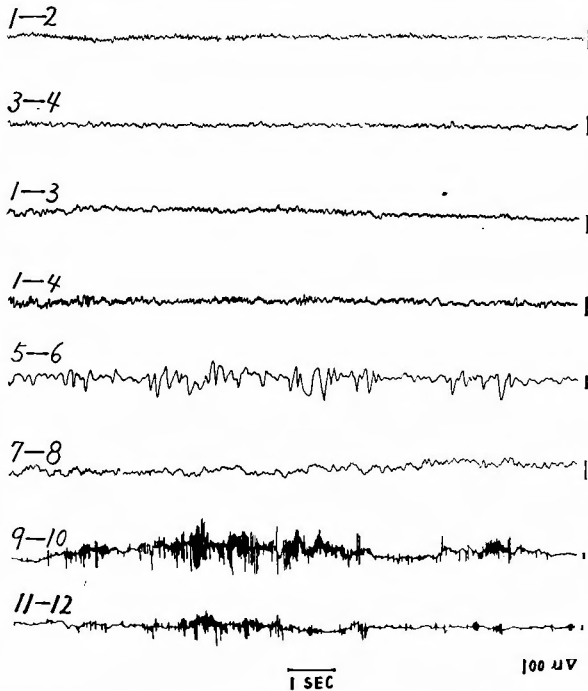
On the 265th day after the injection without any predisposing moment, myoclonic movements with tonic fits, occurring nearly every 30 seconds and lasting for 3-5 seconds, were noted almost in every part of body especially in face and in right upper and lower limbs. These convulsions had lasted off and on for about 58 hours until the animal died. During the seizure, animal crouched and postural reflex was extinguished entirely. The pupils were dilated slightly, the pinna reflex and the pupillary reflex were present, and the sneeze reflex by stimulating septum nasi also was preserved completely.

The surface EEGs recorded from various regions showed mainly 14 to 40 p. s. fast waves superimposing 6 to 10 p. s. ones both being below $50 \mu V$. and no seizure discharge could be noted anywhere.

While, the deep electrogram recorded from the adjacent part of the injected pontine reticular formation consisted of sharp waves with or without 3 to 6 p. s. slow waves, and close simultaneity could be noted between the appearance of sharp waves in deep record and abnormal discharge of muscle in EMG. In the deep record from mesencephalic reticular formation, fast waves dominated and there were no seizure discharges appearing simultaneously with abnormal discharge of muscle (Fig. 3).

The animal, stimulated by pinching the tail and/or applying the heat to his ear lobe, represented strong tonic contraction and increasing of muscle tonus which was remarkable in flexor muscles.

At this time, in the deep electrogram recorded from pontine region, increasing

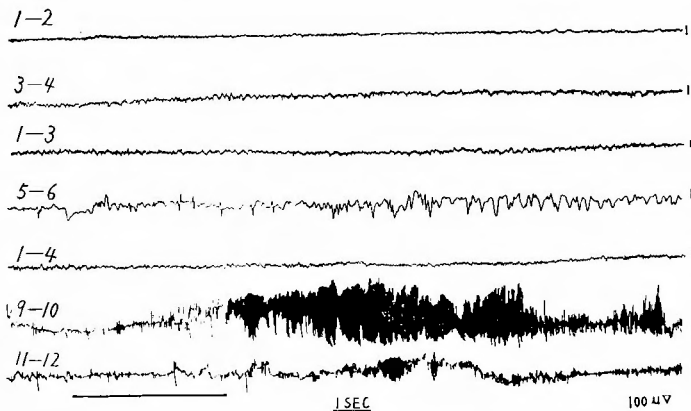
Fig. 3 Surface and deep electrograms recorded during seizure from cat No. 33.

1-2: 3-4: 1-3: 1-4: Surface EEGs.

5-6: Deep record led bipolarly from the adjacent structure of injected region and 7-8: from mesencephalic reticular formation.

9-10: EMG recorded from right m. biceps brachii and

11-12: from right m. triceps brachii.

Fig. 4 Tendency of "reflex epilepsy" was noted in cat No. 33.

Line drawn under EMG tracing indicates the duration of stimulation by applying heat to the right ear lobe.

of sharp wave component and other abnormal findings were perceived, but in the surface EEGs remarkable changes were not elicited by the stimuli (Fig. 4).

Generalized tonic-clonic convulsions were induced by intravenous injection of 5% metrazol in a dose of 0.15 cc. Then the surface EEGs represented the high voltage rhythmic discharge which resembled very much the electroencephalogram taken during a grand mal seizure in man, whereas the deep record showed reinforcement of fast wave component (Fig. 5).

(2) Case 18

0.08 cc of a. c. was injected into the middle level of the left half of pons (Fig. 6).

Fig. 5 Grand mal like seizure was induced by metrazol injection of subconvulsive dose.

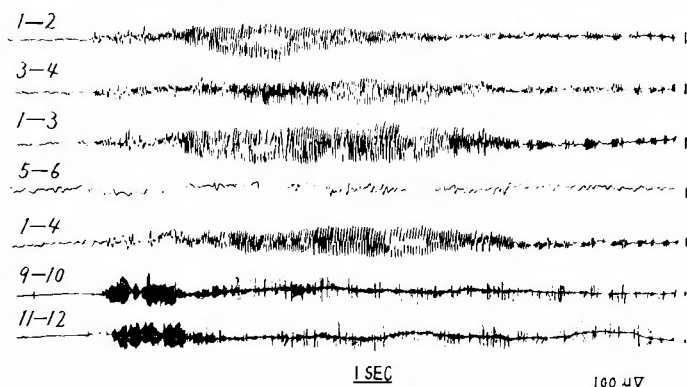


Fig. 6 Transverse section of the pons showing the greatest extent of the lesion in cat No. 18.



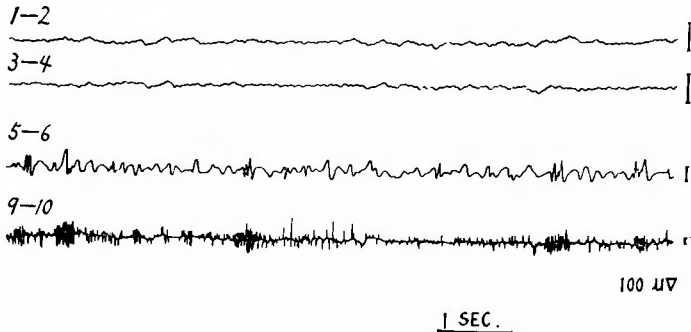
60 days after the injection, strong tonic convulsion superimposed by fine clonic spasms occurred, and lasted for about 56 hours. Responsiveness to nociceptive stimuli remained normal. Remarkable tachypnea probably due to the excitation of respiratory center stimulated by the firing focus was observed.

EEGs recorded during the seizure showed low voltage fast activities (mainly 20 to 30 p. s. below 20 μ V.), while the deep record consisted of "multiple-spikes-and-wave complex" and "spike-or sharp-and-wave complex" (Fig. 7).

(3) Case 58

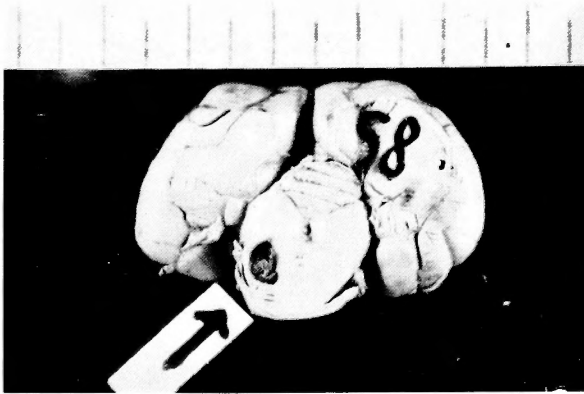
138 days after the injection of 0.12 cc of a. c. into the left rostral level of pons, the myoclonic convulsions with tonic fits occurred, and lasted for about 24 hours until the animal was sacrificed (Fig. 8).

Fig. 7 Electrograms recorded during seizure from cat No. 18.



Surface EEGs (1-2:3-4) revealed mainly 20-30 p. s. fast waves below 20μ V. In deep record (5-6), short bursts of 2 or 4 spikes followed by high voltage slow waves were observed.

Fig. 8 Transverse section of the pons showing the greatest extent of the lesion in cat No. 58.



On the day before onset of seizures, the animal became very excitable and whenever he was given photic and/or auditory stimuli, myoclonic twitches were elicited in the left half of face and right upper limb (Fig. 9).

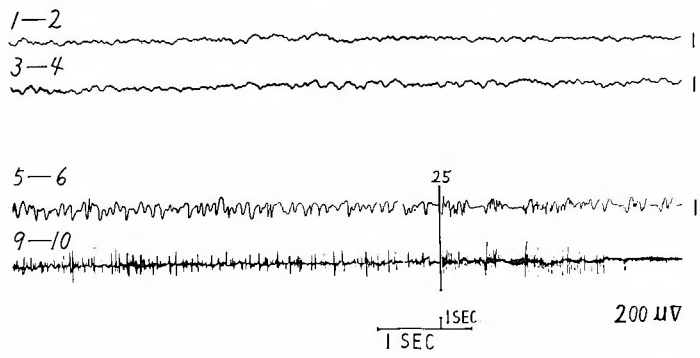
(4) Case 61

0.12 cc of a. c. was injected into the middle level of the left half of pons (Fig. 10).

Immediately after the injection, the animal fell into semicoma for about 5 minutes and a half, but any change of behavior had not been perceived, until the recurrent tonic-clonic convulsions occurred on the 22nd day.

As the animal began to reveal convulsion, he gradually developed tachypnea, and concurrently tonic state almost in every part of body, then fell down after a mew, and brief unresponsive state preceded the onset of grand mal seizures. Remarkable salivation and micturition took place, but terminal sleep did not.

Fig. 9 Electrographic changes recorded during seizure from cat No. 58.

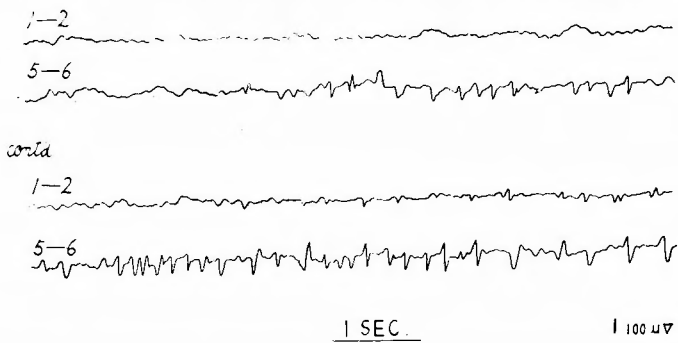


Deep electrogram (5-6) consisted of spike or sharp waves with high voltage slow waves, but in this case, close relationships could occasionally be observed between spike discharge and myoclonic twitches.

Fig. 10 Transverse section of the pons showing the greatest extent of the lesion in cat No. 61.

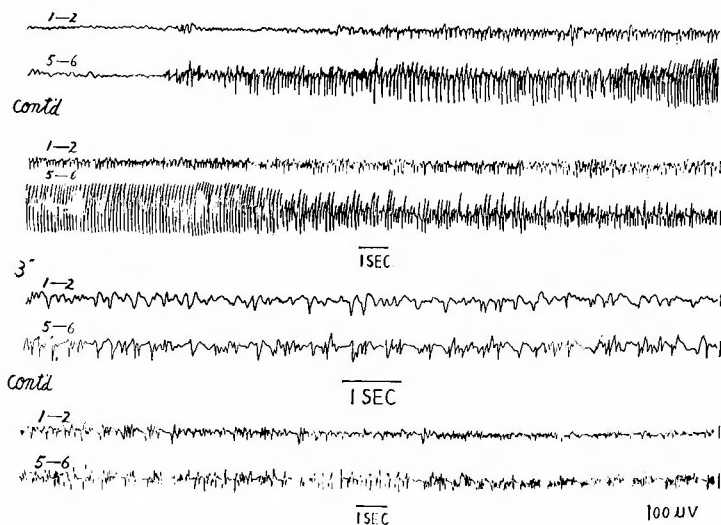


Fig. 11 ECG and deep electrogram recorded from cat No. 61 showing tonic convulsions.



And at the tonic stage before the animal fell down, spike discharge could be noted only in the deep record (Fig. 11), and when grand mal seizure came, 8 to 10 p. s. rhythmic series of spikes were observed in the surface as well as in the deep record (Fig. 12).

Fig. 12 ECG and deep electrogram recorded from cat No. 61 showing grand mal like seizures.



From 8 to 10 p. s. rhythmic series of spikes were observed in both surface and deep records.

3) Metrazol activation

We never tried to provoke seizures in a. c. animals by injection of metrazol (pentamethylene-tetrazol), but we observed the modification of the type of myoclonic convulsions occurring spontaneously in a. c. animals, by injecting metrazol during the seizure. For the explanations of this fact some fundamental experiments were carried out.

A. Electrographic changes with metrazol in normal cats.

Many reports have been presented concerning activation of EEG with metrazol (KAUFMAN et. al 1947, CURE et al. 1948 and others).

In the present experiment, electrographic changes of pontine region with metrazol were studied.

In the deep record, by gradual intravenous injection, there appeared at first the low voltage rapid activities, followed by a clear cut synchronized 4 to 6 p. s. waves (MTEEG) and then high voltage rhythmic discharge. Such electrographic transformations were observed concurrently in the surface as well as in the deep record, but as a whole, changes in the deep record were not so striking as in the surface EEG, that is, spike discharges were fewer in the former and their amplitudes were lower (Fig. 13).

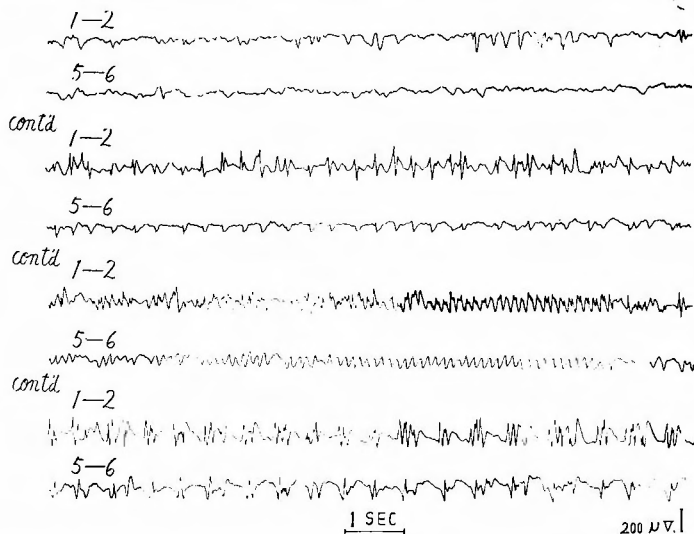
B. Metrazol activation in cats after section at the junction of pons with midbrain.

Gradual intravenous injection of metrazol caused the so-called pontine animal to raise generalized tonic-clonic convulsions.

However, metrazol threshold of such animals was much higher than that of intact animal.

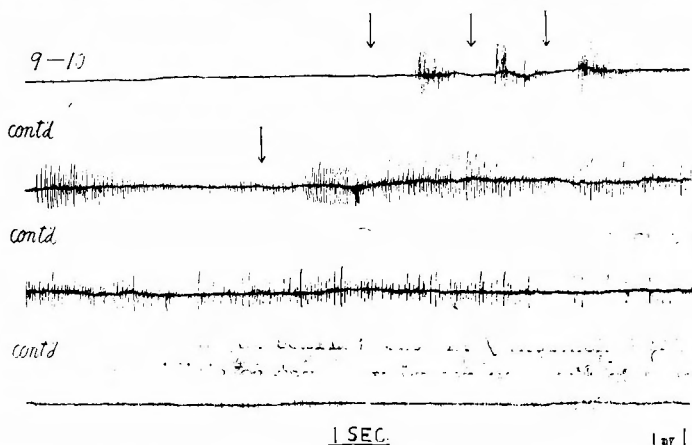
The presence of cerebellum mattered little in the change of the metrazol threshold. And in the so-called pontine animal, seizures were readily provoked by auditory and photic stimuli (to say nothing of pain stimuli) (Fig. 14).

Fig. 13 Electrographic changes induced by metrazol injection in normal cat.



Ten % metrazol had been injected continuously at the rate of 100 mg per min. until convulsion took place. In a dose of 0.45 cc, seizure discharge was noted concurrently in surface as well as deep records. But spike discharges were less remarkable in the latter.

Fig. 14 Changes of EMG induced by metrazol injection in so called "pontine animal".



Convulsions occurred in a dose of 0.75 cc. At arrow animal was stimulated by pinching the tail.

DISCUSSION

1. Changes of EEG during coma induced by inoculation of a. c.
It has been described that in the EEG in the stage of unconsciousness organized

delta activity of high voltage was characteristic (HILL 1950, STRAUSS, OSTOW and GREENSTEIN 1952).

In cases of coma as the result of bilateral destructions of the ascending reticular activating system in the brain stem, high amplitude slow waves are also known to be characteristic (FRENCH and MAGOUN 1952).

It has been reported that following the injection of a. c. into the subcortical structures and/or into the upper brain stem, there appears immediately a marked electrical depression with low voltage slow waves in the entire ipsilateral hemisphere, and also in the contralateral side as well (POPE, MORRIS and others 1947), though fast waves were sometimes seen by injections into basal ganglia especially into thalamus (FEATH et al. 1957).

Of special interest is the fact that the injection of a. c. into the pontine region made a large number of animals fall into transient coma with desynchronized electrograms comparable to what is seen in "arousal".

Besides our patient of pontine epilepsy, by which we have been stimulated to undertake the present study, there are in the literature reports of some cases that had lesions in pons and fell into coma, without showing any organized delta activity, for instance, a case of pontomesencephalic hemorrhage reported by G. POGGIO (1953), a case of infiltrating glioma of lower pons by H. GASTAUT (1954) and a case of atrophy of pontine region due to the failure in vertebral angiography (ARNE LUNDERVOLD et al. 1956). One may also recall the report of LINDSLEY, BOWDEN and MAGOUN in 1949, that EEGs of unanesthetized cats after section at the junction of pons with midbrain revealed activation pattern (low voltage fast activity), which was more pronounced than in intact unanesthetized cats (RHEINBERGER and JASPER, 1937). Similar change of EEG may occur in acute destructive lesion in man's pontomesencephalic region.

In our laboratory SAKATA (1957) and MATSUNAGA (1959), injecting nicotine into the brain stem of unanesthetized cats, observed transient coma with desynchronized EEG, MORIYASU (1959), injecting the same agent into medulla oblongata, and IKUSHIMA (1956), destroying mesencephalic reticular formation by injection of diluted sublimate solution, obtained transient coma accompanied with desynchronized EEG preceding the appearance of such synchronized pattern as was described by MAGOUN and co-workers.

ARAKI, attending especially to disturbance of consciousness accompanied with fast waves, has presumed that the coma showing fast waves is to be distinguished from one showing slow waves.

2. Mechanism of occurrence of coma immediately after a. c. injection or at the time of pontine epileptic seizure.

Normal functioning of brain stem reticular activating system has been said to be indispensable for the maintenance of consciousness. That is, if this system is destructed bilaterally and largely, animals fall into coma and show high voltage slow activities (FRENCH and MAGOUN 1952): If it is stimulated, drowsy animals awake and ECG shows low voltage fast waves (MORUZZI and MAGOUN 1949).

Their findings and ours seem to be incompatible with each other. But FRENCH and MAGOUN's conclusion was based on the observations done at a chronic destructive stage. It is supposed that acute experiment especially with destructive procedures is scarcely free from accompanying excitatory mechanism.

According to MAGOUN (1944) and MAGOUN & RHIENES (1946), medial bulbar structure exerts an inhibitory influence upon spinal motor activity, whether it is voluntary or reflectic.*

It seems possible that the activation of this inhibitory system gives rise to "unresponsiveness" which we have applied as the criteria of coma. Thus for the occurrence of coma immediately after a. c. injection or at the time of experimental pontine epileptic seizure, the following assumption may not be unreasonable: In the pontine reticular system and its adjacent structures where a. c. is or had previously been injected, abnormal excitation takes place, so that the animal shows desynchronized EEG, while responsiveness to nociceptive stimuli can be impeded as the sequence of the inhibitory effect on the spinal reflexes. Man can not detect any motor phenomenon of alertness in such an animal. Thus the animal is regarded as being in coma.**

3. Seizures induced by a. c.

In all but 2 cases among 9, seizures were not of grand mal pattern but of persisting myoclonus pattern intermingled sometimes with tonic fits which resembled both tonic mesencephalic seizures (PENFIELD, ERICKSON 1941) and myoclonic seizures (LENNOX 1944) in man. Moreover, seizures closely resembled the generalized jerks described by DAWSON (1947) in that the jerks could be provoked by sensory stimulation.

Early workers had observed a close relationship between the EEG discharge and the myoclonic twitches in patients with generalized myoclonic seizures (GRINKER, SEROTA and STEIN 1938; DAWSON 1946; KUGERBERG 1954 and others), but PENFIELD and JASPER (1954) pointed out that in many cases of*** "epilepsia partialis continua" no electrographic abnormality is recorded with each myoclonic jerk, suggesting the possibility that a subcortical motor system is primarily responsible for this jerk.

As for the electrograms recorded during the seizure showing myoclonic or tonic convulsions, seizure discharge was not perceived in the surface EEG, as well as in the deep record from mesencephalic reticular formation in any case, and low voltage fast waves were noted as the dominant pattern in many cases.

* The details of control mechanisms remain unsolved. MORIYASU (1959) in our laboratory reported that such MAGOUN's general descending inhibition was seen only in animals in suitable depth of anaesthesia.

** Influence of brain stem stimulation upon "final common path" in unanaesthetized cat has been investigated by us using microelectrode technique. The result is to be published elsewhere in detail by SASAKI, NAMIKAWA and MORI.

*** "Epilepsia partialis continua" (KOJEWNIKOW 1895) or "continuing local motor seizure" (PENFIELD, JASPER 1954) 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. The seizure induced by the injection of a. c. into pons differed from this KOJEWNIKOW-type in that jerks occurred 1) synchronously in almost every part of the body, and 2) not continuously, accompanied by remarkable tonic fits. Thus in this report this term was not used.

In two cases showing the grand mal pattern, so long as the seizure was tonic, no seizure discharge could be perceived in the surface EEG, and it was only when the seizure developed into the grand mal pattern that rhythmic series of spikes were revealed.

These results indicate that:

(1) Discharge arising from the pontine epileptogenic lesion produced by a. c. does not spread to cortex, but may be limited to the adjacent neuronal structures.

(2) And cortical circuits may not be involved in the mechanism of myoclonic and/or tonic convulsions.

(3) EEG desynchronization is likely to be due to excitation of the reticular system stimulated by the firing focus.

(4) It is also characteristic that the seizure could be provoked readily by sensory stimulation. It is considered that activation of the latent epileptogenic focus took place, as the sequence of the excitation of the reticular system in which the focus existed, by naturally transmitted nerve impulses.

In the patient of pontine epilepsy, the seizures were precipitated only by pain stimuli, probably because pain stimuli are the most effective to stimulate the reticular system. In our present animal experiments as well, seizure could be elicited more easily by such strong stimuli as "pinching on the tail or heating the ear-lobe".

4. Comparison of electrographic and behavioral changes observed in clinical pontine epilepsy to those in a. c. animals.

The characteristics of the clinical pontine epilepsy previously reported may be summarized as follows: 1) The fit could be caused instantly by pain stimuli. 2) First he fell into coma for a while, 3) then there came tonic contractions or intermittent twitchings. 4) Interseizure EEGs showed low voltage fast waves both in the period of coma and in the following period of convulsions.

On the contrary, the behavioral and EEG features in a. c. animals may be summarized as follows: Immediately after the injection of a. c. into pons, the majority of animals fell into transient coma accompanied by an desynchronized EEG, but no convulsion took place at this moment in any case. While the convulsions induced in the later stage by pontine a. c. focus, exhibited tonic and/or myoclonic convulsions very similar to those in clinical pontine epilepsy.

Interseizure EEGs in a. c. animals revealed low voltage fast waves and seizure could be elicited by sensory stimulation. But responsiveness to nociceptive stimuli was not much disturbed during seizure in a. c. animals on the contrary to pontine epileptic patient.

After all, the epileptic seizure in a. c. animals resembled the clinical "pontine epilepsy" to some extent but not entirely. As to the reason of this discrepancy, nothing definite can be said at present.

5. Metrazol activation

Convulsion of myoclonus pattern was turned into that of grand mal pattern readily by subconvulsive metrazol injection. In so called pontine animal too,

recurrent tonic-clonic convulsions could be provoked.

These facts may throw a doubt that, in our experiments, the deficiency of quantity of a. c. might have caused convulsion of myoclonus pattern instead of that of grand mal pattern.

But we injected a. c. containing 2-12 mg Al. It is generally estimated that the amount of a. c. indispensable for producing epileptic focus in animal ranged from 0.1 to 0.6 cc, aluminum content being between 0.4 and 5.4 mg (KOPELOFF et al. 1955).

AJMONE-MARSAN and MAROSSERO, in 1950, in cats, suggested from their findings of electrocortico- and electrochordographic studies that mesencephalic transection abolishes every effect of metrazol on the spinal activity, leaving the convulsive activity in the cortex unchanged, even with supraliminal doses of the drug. From this fact, it was reasoned by JASPER (1954) that metrazol does not act effectively as convulsant on structures below the level of diencephalon. While KIRSTEIN et al., in 1952, reported that metrazol, acting on various levels of neuraxis from cortex down to spinal cord, increases the intraneuronal activity.

In the present study, though the convulsion of grand mal pattern could be provoked in the so-called pontine animal, but from the facts that much more amount of metrazol must have been injected into pontine animal than intact cat and seizure discharge in electrogram was less remarkable in pontine region than in cortex, we believe, metrazol, injected intravenously, shows different affinity between cerebral cortex and pons, the former being the principal site of action.

Moreover, cerebral cortex, by secondary activation from pontine firing focus and by action of a part of a. c. which had flowed back along the track of injection and adhered to cortex, must have increased its sensibility.

Owing to these facts, it is considered that metrazol, injected into a cat showing myoclonic or tonic pattern seizure, chiefly acts upon cerebral cortex rather than on firing focus of pons, and therefore, subconvulsive dose of it provokes cortical metrazol seizure, i. e. grand mal pattern. The experimental fact that though remarkable seizure discharges were found in the surface EEGs, changes could hardly be observed in the deep record (Fig. 5), testifies this assumption of ours.

SUMMARY

Alumina cream prepared by KOPELOFF's method (1942) was injected only once into the one half of pontine region.

Immediately after injection, EEGs revealed, in majority of animals, the desynchronization followed by the pattern of low voltage slow activity. During the period of EEG desynchronization, animals fell into transient (about 3-10 minutes) coma.

In 9 cats out of 34 (ca. 26%), seizures developed 22-265 days after the inoculation of alumina cream. In all but 2 cats among these 9, seizures were not of the grand mal pattern but of the persisting myoclonus pattern intermingled with tonic fits and resembled both tonic mesencephalic seizures (PENFIELD, ERICKSON 1941)

and myoclonic seizures (LENNOX 1944) in man. During seizure responsiveness to nociceptive stimuli was not much disturbed in these animals.

Surface EEGs recorded during seizure showed mainly 20-40 p. s. fast waves below 50 μ V. in many cases, and no distinct seizure activities in any case, while deep electrograms led bipolarly from the pontine reticular formation revealed spike or sharp waves associated sometimes with slow waves, occurring synchronously with myoclonic twitches.

These fits could be elicited or precipitated readily by sensory stimulation.

It seems that the discharge arising from the pontine epileptogenic focus produced by alumina cream may be limited to the local neuronal structure around the lesion and the cortical circuits may not be involved in the mechanism of myoclonic and/or tonic convulsions.

These experimental data, we believe, may largely be in accord with the neurological and electrographic findings in the patient of pontine epilepsy which had already been reported by ARAKI and others (1956). The only difference was the inconsistent occurrence of the disturbance of consciousness (unresponsiveness to nociceptive stimuli) during a. c. seizures.

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アルミナクリームによる橋性癲癇の実験的研究

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実験的に橋性癲癇を作る目的で, KOPELOFF (1942)の方法により, アルミナクリームを製作し, 之を猫の一側橋に注入, その経過を観察した。

注入直後, 大多数の動物は皮質脳波及び注入部附近からの深部脳電図の desynchronization を示すと共に, 一過性 (約3~10分) の昏睡に陥つたが, 痙攣を伴つた例は無かつた。

34例中9例がアルミナクリーム注入後22~265日で、痙攣発作を惹起した。2例を除く他の全例の痙攣は、大発作の型をとらず tonic fits を伴う persisting myoclonus 型で、人間の tonic mesencephalic seizures (PENFIELD, ERICKSON 1941) と myoclonic seizures (LENNOX 1944) の両者に似ていた。痙攣は知覚刺激により容易に誘発され、痙攣時の皮質脳波は、大多数が低電位速波で痙攣波の出現は1例にも認め得なかつた。一方橋網様組織からの深部記録は、筋搐搦

と大略同期する spike 又は sharp waves と高振幅徐波よりなつていて、痙攣が大発作型に発展して始めて皮質脳波に hypersynchronous neuronal discharge が認められた。

之等の所見は、アルミナクリームにより作られた橋の癲癇性焦点よりの放電は、皮質に波及せず注入部附近に止り、皮質は強直性又は筋搐搦性痙攣の発生機構に関して第一義的意義を有しないことを示すものである。

以上の成績は、荒木及び協同研究者により報告された probable "pontine epilepsy" (1956) の患者の示した神経学的及び脳波学的所見と大体に於て一致するが、アルミナクリーム動物の痙攣発作中の侵害反射に対する反応性の障害の程度は、臨床例に於て認められた程著明でなく、この点が人間に於ける橋性癲癇とアルミナクリーム動物のそれとの異なるところであつた。