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ACUTE AND CHRONIC DISTURBANCE OF CONSCIOUSNESS AFTER MESENCEPHALIC DESTRUCTION BY MEANS OF ELECTROCOAGULATION

by

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INTRODUCTION

Over the past fourteen years a series of experiments has been carried out in our laboratory with regard to experimental disturbances of consciousness under the name "coma puncture". The results indicate that the central grey matter of the midbrain, particularly in the region extending from the oculomotor to the trochlear nucleus may be the most important region in the maintenance of consciousness. However, severe experimental disturbances of consciousness in the past have been transient lasting only from a few minutes to 20 minutes in almost all cases. It is very difficult to compare such short experimental disturbances of consciousness with coma in patients having severe head injuries in whom coma may last from a few hours to a few days or longer.

About ten years ago TAKETOMO caused a prolonged coma (lasting about 50 minutes) in a rabbit with electrocoagulation of the ponto-mesencephalic region using the old machine of Bovie. Thus in the present study, we have electrocoagulated the mesencephalic region in cats using the Bovie's machine in order to induce prolonged unconsciousness of half an hour or more duration. We have studied the behavioral and EEG changes through the entire survival periods of the experimental animals in order to better understand prolonged coma. In addition we have studied the difference in the effect of destruction of the central grey matter of the midbrain, which we have felt to be essential for the maintenance of consciousness, and the destruction of the reticular formation of the midbrain, which MAGOUN has stated is the seat of the regulating mechanism of consciousness.

Definition of disturbance of consciousness is the most important problem in animal experiments of this type. In our laboratory we difine this as follows:

1) Unresponsiveness Ist degree (semicoma Ist degree).

In this state, the postural reflex is somewhat feeble. The searching-reflex to light and sound and the reactive motion phenomenon induced by touch or pressure to the body surface are almost abolished. But the animal still reacts to painful and smell stimuli very well. (GIRNDT II-IV).

2) Unresponsiveness 2nd degree (semicoma 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 sense are of course absent. The reflex to painful 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. (GIRNDT IV-V).

3) Unresponsiveness 3rd degree (coma).

The reflex due to stimuli of nasal tip and septum nasi and the vomiting reflex due to stimuli of pharyngeal mucosa are absent. The corneal reflex, the pupilary reflex, and the pinna reflex are sometimes present. Patellar reflex remains. (Over GIRNDT V).

EXPERIMENTAL METHOD

A mature cat was fixed on a hammock in prone position and the four limbs were allowed to hang down naturally. After installation of the stereotaxic instrument (hang down type) was carried out under ether anesthesia, four silver ball electrodes for recording the EEG were inserted passing through the skull and fixed to the level of dura. Location of the silver ball electrodes were as follows: "1": the anterior part of the left hemisphere, "2": the same as 1 on the right side, "3": posterior part of the left hemisphere, "4": the same as 3 on the right side.

After the cat had awakened fully, electrocoagulation in various parts of the midbrain was carried out. The insertion of the electrode for electrocoagulation was done in two ways. In one the electrode was inserted vertically under the guidance of HORSLEY-CLARKE'S stereotaxic instrument through the parietal hole trephined. In the other the electrode was inserted through an opening in the occipito-atlantoid ligament and then through the 4th ventricle along the aqueduct of the midbrain.

The destroying electrodes consisted of iron-chrome wires of 15cm in length and 0.3mm in diameter, each of which was insulated except for 0.1-3.0mm of the tip by means of specific lacquer (hōrō) or glasstube cover and could be used as a bipolar or unipolar electrode. The destruction of the tissue by electrocoagulation was made with an electric current of 90-100 volts and 80-100MA or more and during the period of 1 second- 1 minute. In some experiments an electric resistance of 1.5-3 kiloohms was used.

The degree of disturbance of consciousness due to these electrocoagulation was examined according to criteria described above and behavioral and EEG changes were studied throughout the survival time of the animal.

After the death of the experimental animals, the brain stems were fixed in alcohol absolutus, packed in celloidin, sectioned serially and the areas of destruction were confirmed by histological examination using NISSL stain, myelin sheath stain and iron-carmine stain. Anatomical guidance was obtained from WINKLER and POTTER (1914), JASPER and AJOMONE-MARSAN (1955).

RESULTS

Electrocoagulation was performed on the central grey matter of the midbrain in 21 cats, the reticular formation of the midbrain in 7 cats, both of them in 5 cats, lamina quadrigemina in 5 cats and other parts in 14 cats, that is in a total of 52 cats. The experimental animals are divided into a coma group and a non-coma group.

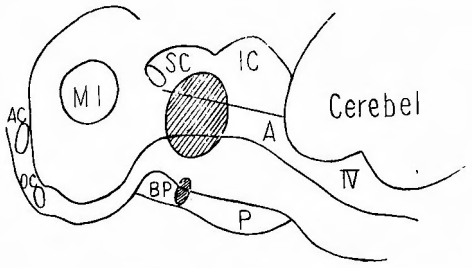

Fig. 1 Midsagittal reconstruction of the brain stem showing the area of lesions (shaded) from which behavioral unresponsiveness 1-3 resulted.

A) Coma group (Fig. I, 2 and 3)

Abbreviations for all figures are as follows: A-aqueduct, AC-anterior commissure, BIC-brachium of inferior colliculus, BP-basis pedunculi, BRC-brachium conjunctivum, CER-cerebellum, GC- substantia grisea centralis, IC-inferior colliculus, IP-interpeduncular nucleus, LL-lateral lemniscus, LG-lateral geniculate body, MG-medial geniculate body, MF-medial longitudinal fasciculus, MI-massa intermedia, ML-medial lemniscus, OC-optic chiasma, P-pons, PC-posterior commissure, RF-reticular formation, RN-red nucleus, SC-superior colliculus, SN-substantia nigra, IV-fourth ventricle, L-left side of the brain, R-right side of the brain.

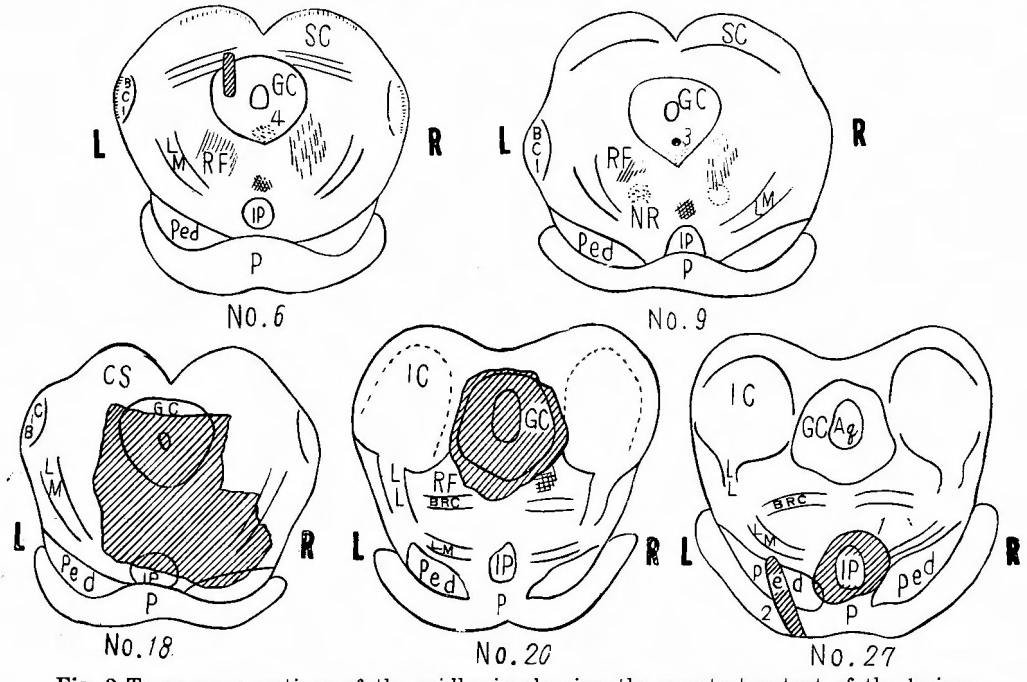

Fig. 2 Transverse sections of the midbrain showing the greatest extent of the lesions (shaded areas).

Six cats became comatose immediately after electrocoagulation. Whether or not the animal fell into coma initially, no animal fell into coma later for the first time or again during the survival period.

In the 6 comatose cases, coma occurring in 2 cats was transient as follows. Cat No. 6 fell into coma for 15 minutes and semicoma for the succeeding 10 minutes. Cat No. 9 fell into semicoma for 7 minutes. In both there was a little lesion in the central grey matter.

The remaining 4 comatose cases were as follows.

Cat No. 18 fell into coma for 55 minutes and then recovered its noci-reflexes

for a while. Then it became comatose again and died 5 hours after electrocoagulation. This animal had almost all the region of the central grey matter and a large portion of the reticular formation of the midbrain destroyed.

Cat No. 20 fell into coma for 2 hours and died without awakening accompanied by a tonic spasm of the whole body immediately before death. This animal had almost all the region of the central grey matter of the midbrain extending from the oculomotor to the trochlear nucleus destroyed.

Cat No. 27 was electrocoagulated 2 times. At first this animal had the nucleus interpeduncularis and its surroundings destroyed. At this time, this animal did not show any disturbance of consciousness. Eight days later re-electrocoagulation was done in the portion of crus cerebri. Immediately after this experimental destruction, this animal fell into coma and died one hour and 20 minutes later without awakening, exhibiting extreme myosis, Cheyne-Stoke's respiration and clonic spasm in the left limbs. From autopsy findings the death was apparently due to subarachnoid bleeding.

A detailed description of the change of behavior in cat No. 50 (male, 3Kg) is given as follows.

Before electrocoagulation he was wild, snarled and cried in a raging manner and his noci-reflex was completely normal. There was no change in behavior with insertion of the electrode. The electrocoagulation was carried out for 10 seconds. During this period of electrocoagulation, tonic spasm of the whole body and mydriasis appeared. Immediately following electrocoagulation he became mild and the corneal reflex, pinna reflex, pharyngeal reflex, reflexes of all four limbs disappeared. The head hung down and the four limbs became flaccid. The animal was unable to avoid the test smoke. All ties were loosened. Fifteen minutes later, the four limbs were flaccid, the escape reflex of all four limbs, the reflex of the tip of the nose to painful stimuli and the corneal reflex were still absent, but the pinna reflex and the pharyngeal reflex reappeared to a small extent and the animal was able to avoid the test smoke. The animal did not mew or move at all. His head remained hung down. Thirty minutes post injury the corneal reflex and postural reflex reappeard and the other noci-reflexes were recovered normally. He was able to walk down from the hammock unaided but his walk was ataxic. At that time the cat did not mew and did not show any interest in food or water. On the 2nd postoperative day, the cat was sitting apathetic to objects or the environment in his cage. He did not mew or show any interest in water or food. His pupils showed moderate dilatation. The pupillary reaction to light was prompt and the noci-reflexes were all normal. When the cat was taken out from his cage, he walked aimlessly and slowly, but by this time his walk was not ataxic. When the nourishment by a stomach tube was done, he raged, bared his teeth and spit out the milk leaked into the pharynx from a bite hole of his feeding tube together with saliva. On the 3rd postoperative day, the animal appeared generally to behave as on the day before, but he was beginning to hide himself slowly if stimulated. Without stimulation, he sat immobile and did not pay attention to anything in his environment. On subsequent days the cat's behavior resembled that described

above until he died on the 8th postoperative day. Throughout the postoperative course the noci-reflexes and postural reflex were maintained. Also the cat showed no evidence of emotion.

The regions destroyed were almost all in the central grey matter of the midbrain in the region extending from the rostral end of the oculomotor nucleus to the caudal end of the trochlear nucleus and the centre of the destroyed area was usually at the level of the caudal end of the colliculus superior (Fig. 3).

Unfortunately it was not possible to record EEGs successfully in the 5 animals which became comatose following electrocoagulation of the mesencephalic central grey matter. The EEG of cat No. 27 (Fig. 4), which fell into coma after the destruction of the crus cerebri, became flat immediately after electrocoagulation. Next occurred a seizure discharge or spike wave followed shortly by spindle bursts, gradually in time these disappeared and the EEG last became entirely flat and continued so without recovery until death.

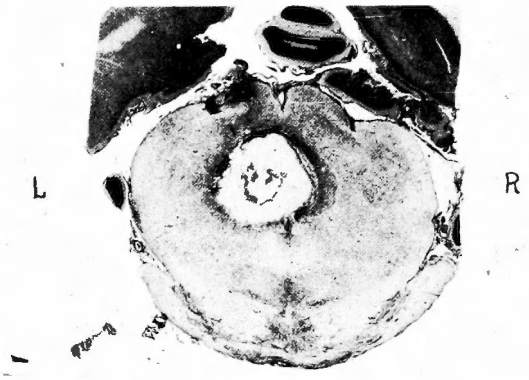

Fig. 3 Transverse section of the midbrain showing the greatest extent of the lesion in cat No. 50. Thionin stain.

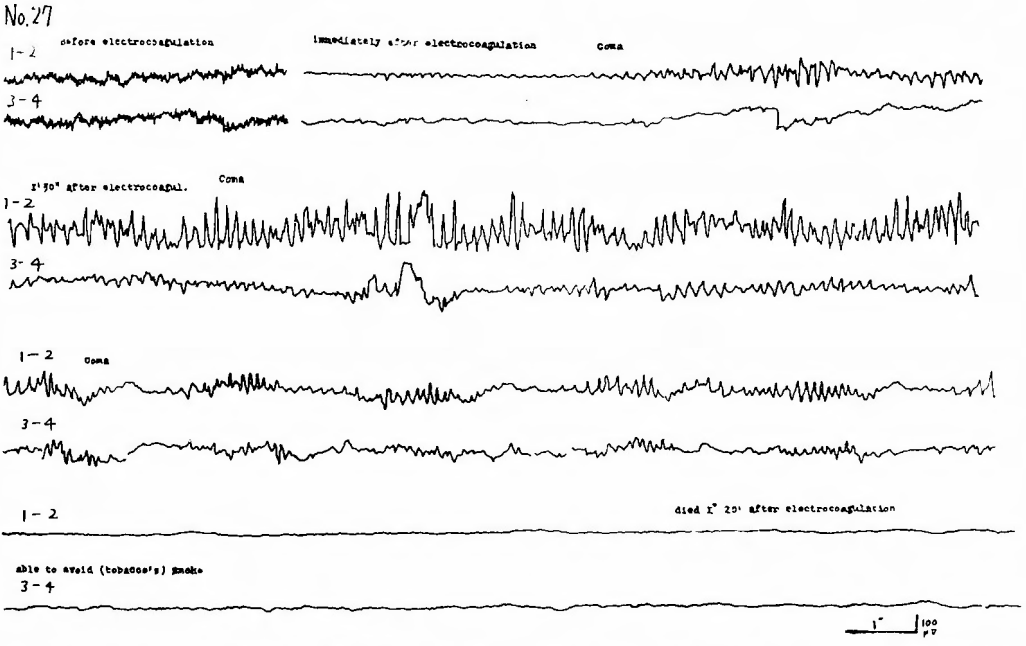

Fig. 4 The recording of EEG in cat No. 27 which fell into coma by destroying crus cerebri and died without waking. Seizure discharge is synchronous with clonic spasm in left limbs.

B) Non-coma group

The 23 animals of the non-coma group lived an average of 5.6 days. The longest lived 12 days. Five animals that lived more than 7 days were recoagulated and in these animals death was thus hastened. Behavioral changes had relation to the degree and location of the midbrain destruction.

1) Those animals in which the central grey matter was largely destroyed. Experiments were done in 9 cats.

Course of the experiment in cat No. 47 (female, 2kg) :

She mewed and moved actively before the operation. There were no behavioral changes seen due to insertion of the electrode. With the onset of coagulation the cat cried once and then became quiet. During coagulation a tonic spasm of the entire body occurred. At that time the pupils became dilated. After operation the animal did not mew and did not move at all. From time to time she licked her lips. The animal seemed to be semicomatose and all 4 limbs were flaccid, but she retained all her noci-reflexes. When released the cat lay down on the floor and had not postural reflex. At times she struggled, but she did not eat and did not respond to visual, auditory, tactile or olfactory stimuli. On the 2nd postoperative day, she laid down herself and at times moved her four limbs as if she tried to walk, but she did not mew nor show any interest in food or water. In spite of warming and nourishing by a stomach tube, the symptoms did not improve and she died on the 4th postoperative day.

In the EEG obtained from this animal, both flattening and spindle bursts occurred. The portion of her brain destroyed was the central grey in the region extending from the rostral end of colliculus sup. to the rostral end of colliculus inf. and the centre of destruction was at the level of the oculomotor nucleus (Fig. 5).

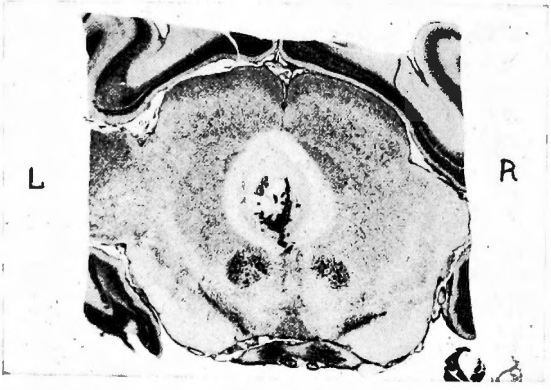

Fig. 5 Transverse section of the midbrain showing the greatest extent of the lesion in cat No. 47. Thionin stain.

The postoperative courses in cats No. 52 and No. 53 were the same as the course of No. 50 of the coma group. After the 2nd day, they licked milk a little if placed before their noses, but they would not drink any more and they died on the 5th and 4th postoperative day respectively. In each cat the portions destroyed were the central grey matter of the midbrain in the region extending from the oculomotor nucleus to the trochlear nucleus (Figs. 6 and 7).

In the EEG obtained from cat No. 53, the fast waves present before operation were flattened immediately after electrocoagulation and then slow waves appeared. Next the spindle bursts appeared intermittently. In the EEG of cat No. 52, the fast waves continued after operation (Fig. 8) and intermittently mixed with spindle bursts.

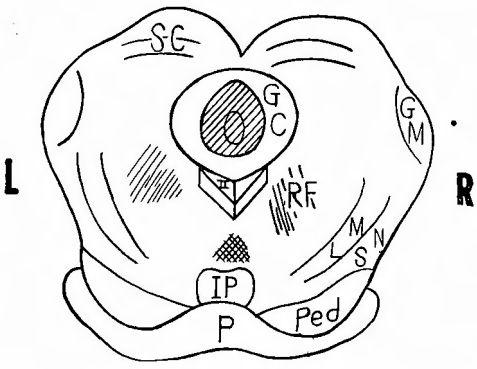

Fig. 6 Transverse section of the midbrain showing the greatest extent of the lesion (shaded area) in cat No. 52.

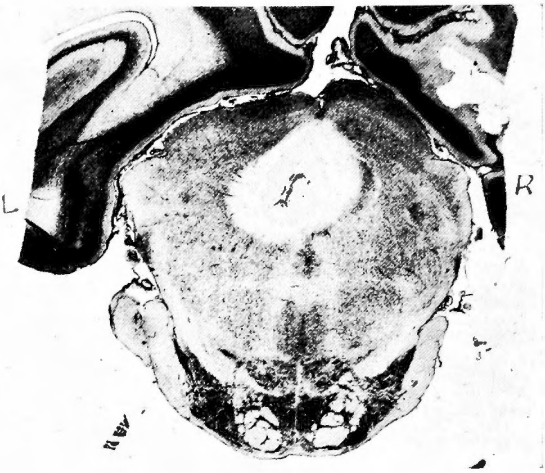

Fig. 7 Transverse section of the midbrain showing the greatest extent of the lesion in cat No. 53. Thionin stain.

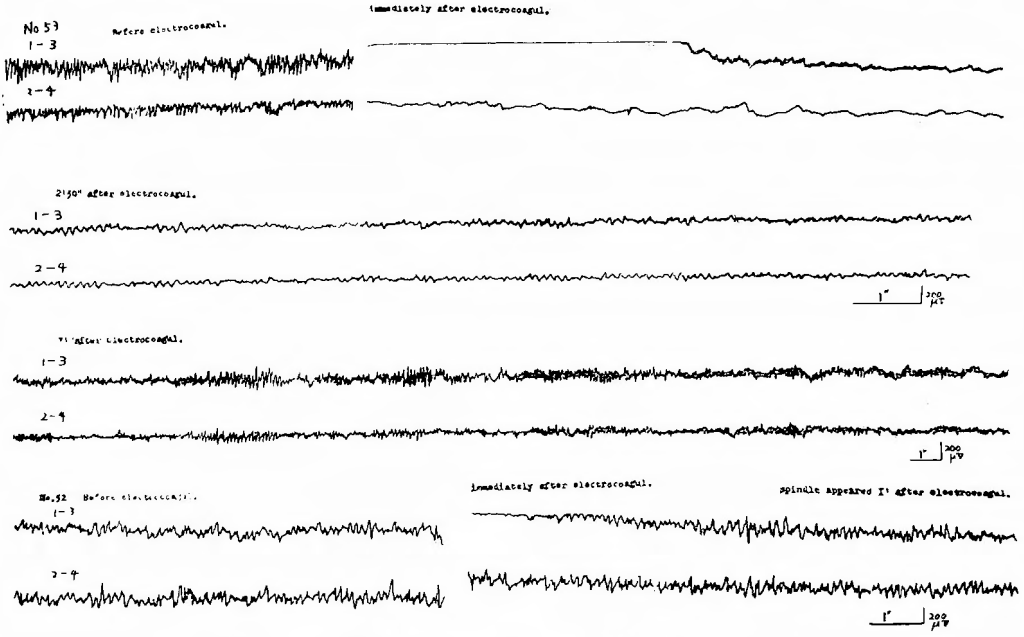

Fig. 8 The recording of EEG in cat No. 53 and No. 52.

Course of cat No. 46 (male, 3. 5kg):

This cat became quiet entirely and seemed to be semicomatose in spite of that he was wild before electrocoagulation. He retained all his noci-reflexes. After 2 or 3 minutes, he began to mew, snarled and became wild as though seeing imaginary menaces. When he was loosened from his fixings, he tried to walk at once, but he could not walk, because he fell down to the right. He lifted his head despite lying down and at the same time he made walking-like or running-like movements in all four limbs, especially in his front limbs. Five minutes later, he sat up and

began to walk and climb up a door. He never showed any interest in food or water. On the 2nd postoperative day he was sitting apathetically, inertly and silently and turned his head to the left, looked up and stared vacantly into space with his eyelids opened. He never mewed unlike the day before. Pupils were dilated on both sides, but especially markedly on the right and his pupillary reaction to light was prompt. All noci-reflexes were retained normally, but he had no appetite. When he was taken out, he walked slowly into the cage and sat silently. On the 3rd postoperative day his condition was unchanged. On the 4th postoperative day his eyelids remained open still, but his eyes showed more evidence of alertness. He stopped to stare vacantly into space, but still did not mew or show any interest in food and water. He died on the 5th postoperative day in spite of nourishment via the stomach tube. The area destroyed was in the region extending from the caudal end of the thalamus to the middle of the colliculus sup. and its centre was in the area in which the aqueduct of the midbrain opens into the 3rd ventricle (Fig. 9).

Though the EEG obtained from cat No. 46 was only recorded on the operative day, low voltage fast waves and low voltage slow waves seen before electrocoagulation became flat immediately after operation and then low voltage slow waves appeared. Shortly afterward low voltage fast waves were mixed in and finally spindle bursts appeared with the low voltage slow waves (Fig. 10).

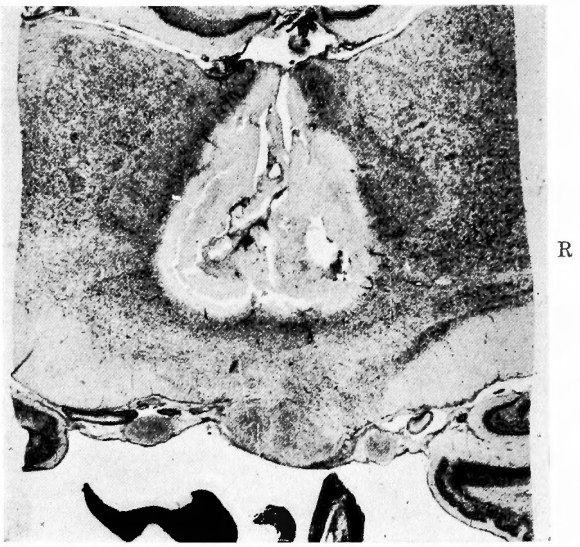

Fig. 9 Transverse section of the posterior diencephalon showing the greatest extent of the lesion in cat No. 46. Thionin stain.

2) Animals in which only a little amount of destruction was done in the central grey matter (Fig. II).

In many of these experiments the cats mewed, snarled and raged on the operative day. That is, they showed an initial excitatory or rage reaction. On the 2nd and 3rd postoperative day the cats mewed very frequently, but did not show any interest in surroundings, food or water, and remained inert. After the 3rd or 4th postoperative day, they began to show appetite and activity little by little. When the 2nd electrocoagulation was done, the marked changes in behavior seen after the Ist electrocoagulation were never seen and postoperative behavior was as before the 2nd electrocoagulation.

In the EEG obtained from cat No. 41, the flattening appeared immediately after electrocoagulation and soon low voltage fast waves similar to those seen before electrocoagulation as well as spindle bursts appeared. On the 4th postoperative

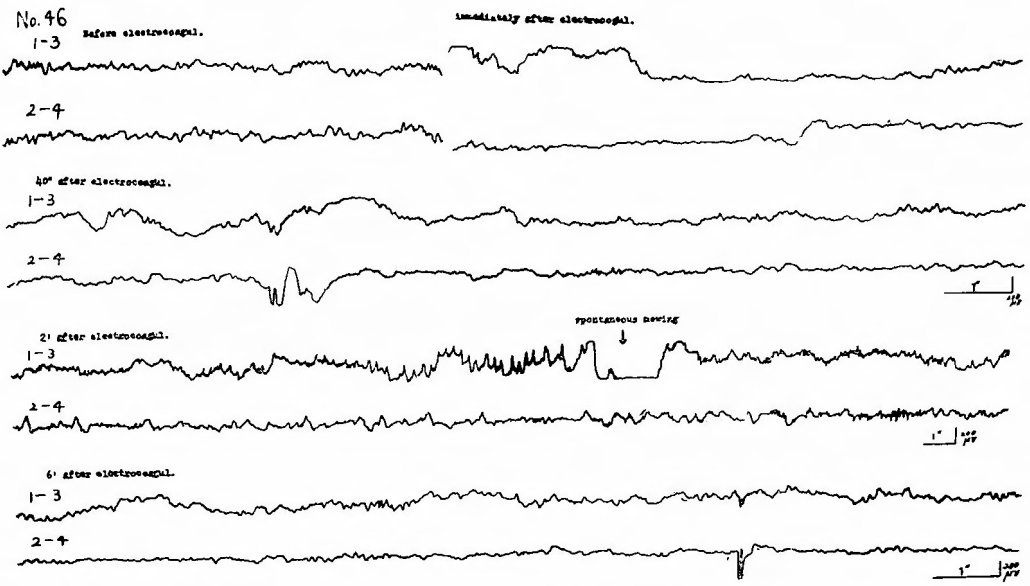

Fig. 10 The recording of EEG in cat No. 46.

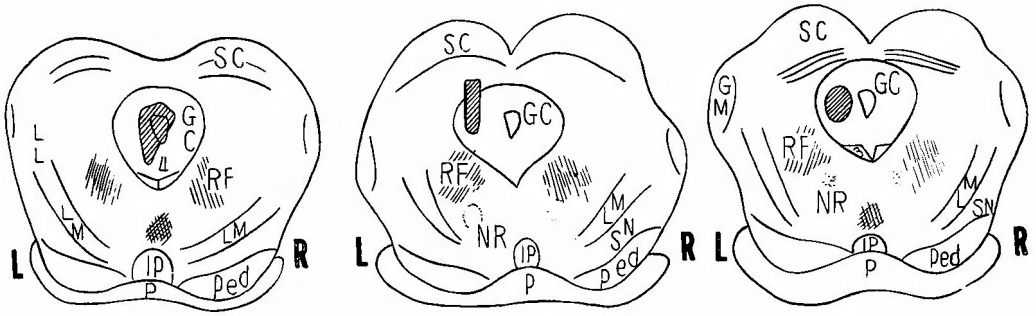

Fig. 11 Transverse sections of the midbrain showing the greatest extent of the lesions.

day the spindle bursts disappeared and slow waves were seen at rest, while low voltage fast waves were seen in the moving state. In the EEG of cat No. 51, the flattening appeared immediately after electrocoagulation for a short time. Then the low voltage fast waves and spindle bursts appeared. In the EEG obtained from cat No. 36, low voltage fast waves seen before electrocoagulation continued and 2 to 3 minutes later spindle bursts appeared (Fig. 12).

3) Animals in which the destruction occurred in the central grey matter and reticular formation of the midbrain (Fig. 13 and 14).

These animals retained the noci-reflexes immediately after electrocoagulation, but they lost the postural reflex and lay down continually hanging their heads inertly as if dead. They all died within 48 hours. In the EEG obtained from No. 54, spindle bursts mixed with low voltage fast waves were seen after electrocoagulation.

In cat No. 30, the central grey matter and the reticular formation of the

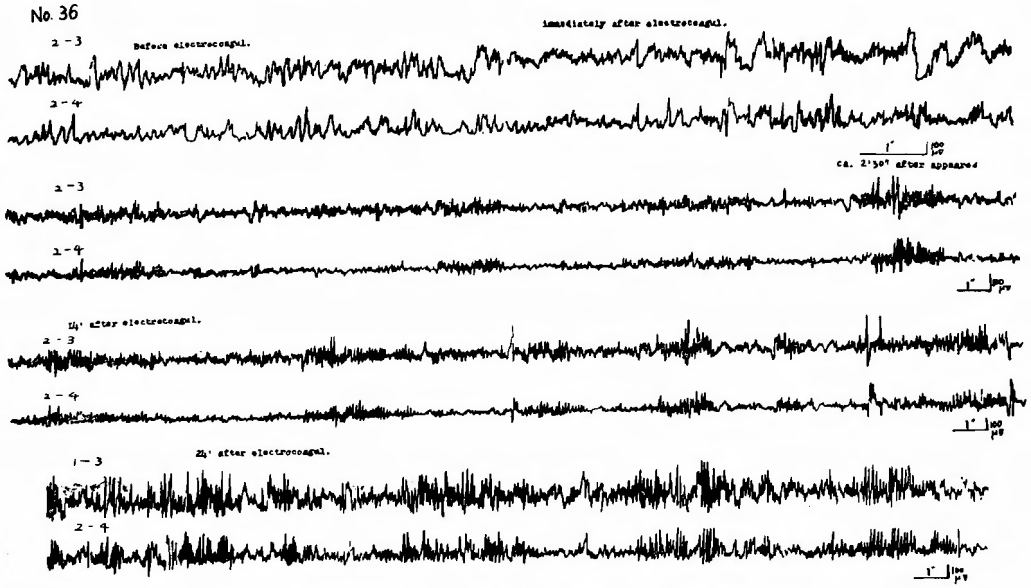

Fig. 12 The recording of EEG in cat No. 36.

midbrain were destroyed slightly (Fig. 15) and this case was not very different from the instances in which only the central grey matter was slightly destroyed as described in 2) in behavior pattern; that is, after excitation the animal showed hypokinesia. In the EEG obtained from this cat, low voltage slow waves mixed rarely with low voltage fast waves were seen before electrocoagulation. After electrocoagulation the low voltage fast waves disappeared. Next the low voltage fast waves appeared again and then spindle bursts appeared. On the 8th postoperative day, low voltage fast and high voltage slow waves appeared mixed and on the 12th postoperative day the low voltage fast waves only appeared (Fig. 16).

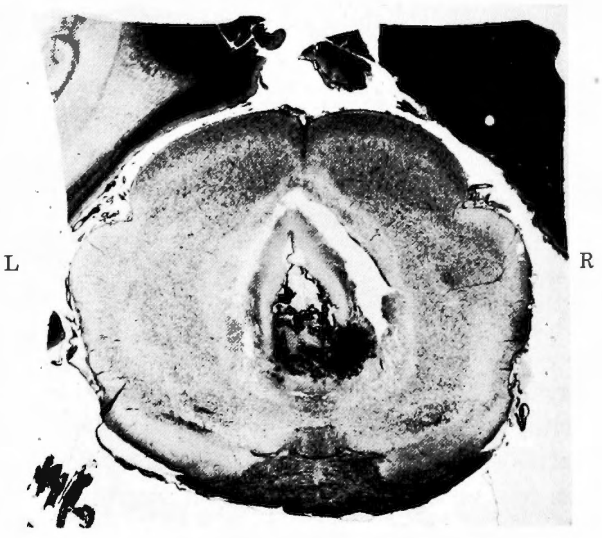

Fig. 13 Transverse section of the midbrain showing the greatest extent of the lesion in cat No. 48. Thionin stain.

4) Animals in which the reticular formation of the midbrain was destroyed.

Course of the experiment in cat No. 28 (female, 4.3kg):

Throughout coagulation the cat's respiration was accelerated, but no spasm occurred and the noci-reflexes were retained after electrocoagulation. The pupils were moderately dilated, and more so on the left than on the right. The cat

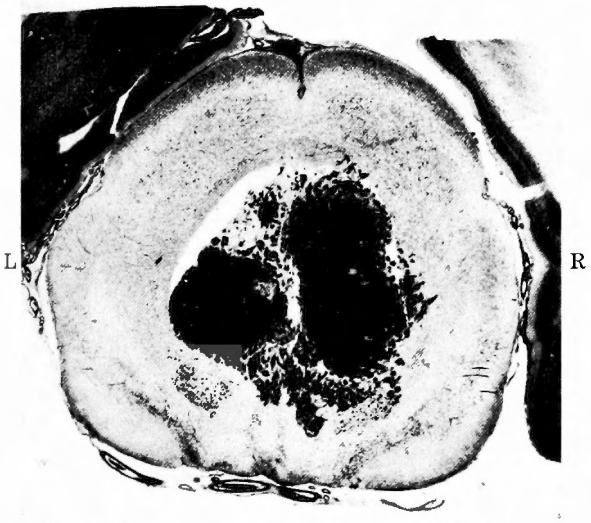

Fig. 14 Transverse section of the midbrain showing the greatest extent of the lesion in cat No. 54 Thionin stain.

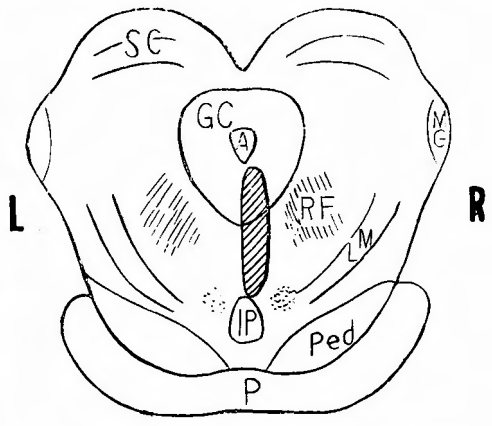

Fig. 15 Transverse section of the midbrain showing the greatest exent of the lesion (shaded area) in cat No. 30.

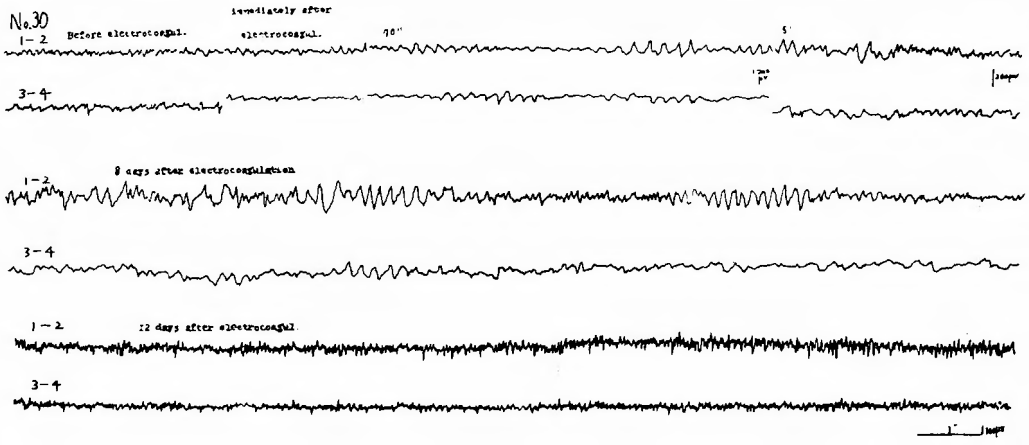

Fig. 16 The recording of EEG in cat No. 30

became very quiet and did not move or mew. She lay down wherever she was placed, lying inertly on the floor and hanging her head down as if she had died, when she was loosened from her ties. Her postural reflex had disappeared. She did not show any interest in food or water. On the 2nd postoperative day she lay where placed in the same posture in the cage as on the day before and seemed unaware of ordinary environmental stimuli. She never moved or mewed and seemed to be dead. Irritation which would cause an immediate cry out from a normal cat, provoked only a feeble movement of the head and a stepping movement of the extremities. But she retained her noci-reflexes. She did not show any interest in food or water. Throughout her survival period, the same behavior continued and

on the 7th postoperative day she died. Study showed severe destruction on the left side of the reticular formation of the midbrain at the level of the oculomotor nucleus (Fig. 17).

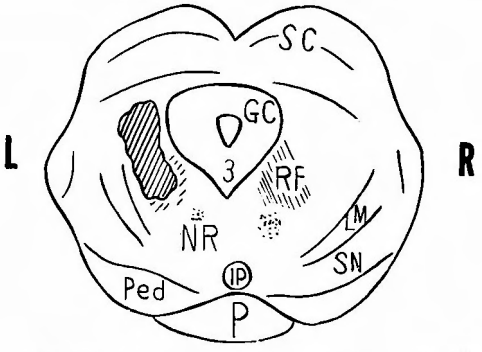

Fig. 17 Transverse section of the midbrain showing the greatest extent of the lesion (shaded area) in cat No. 28.

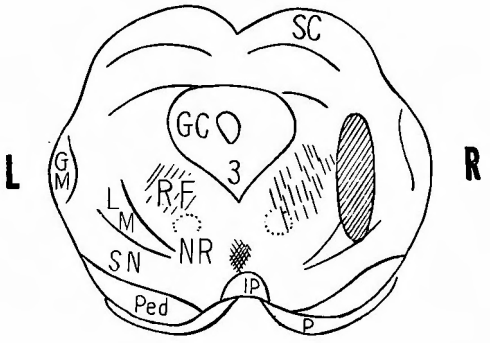

Fig. 18 Transverse section of the midbrain showing the greatest extent of the lesion (shaded area) in cat No. 32.

Cat No. 32 (Fig. 18) mewed and raged continually very much throughout the operation. Muscle tone was rigid and all noci-reflexes were retained. When loosened from fixation, she walked at once and mewed continually. On the 2nd and 3rd postoperative day, she mewed frequently and walked about continually. Since the 4th postoperative day her behavior recovered. Throughout the whole postoperative period, she did not show any interest in food or water. She died on the 9th postoperative day. In the EEG obtained from this animal the flattening appeared immediately after electrocoagulation and in half an hour preoperative low voltage fast waves came out. Some flattening was still present after 24 hours. On the 4th postoperative day, the flattening disappeared and spindle bursts appeared, but on the 6th day the tendency to flattening came out again (Fig. 19).

5) Animals whose brain stems were destroyed in the other areas.

The colliculus sup. et inf., medial lemniscus or interpeduncular nucleus were destroyed in several cases. In these animals on the Ist and 2nd postoperative day following surgery those who still showed the effects of surgery were raging or inactive, sometimes showed anorexia, anisocoria or nystagmus. After about the 3rd postoperative day their behavior became normal and did not show any disturbance of consciousness. In the EEGs, some cases did not show any changes as a result of electrocoagulation but others showed slow waves, flattening or spindle bursts.

DISCUSSION

It has been known for a long time that pathological sleep or severe disturbance of consciousness could be associated with lesions in definite portions of the brain stem. MAUTHNER, in 1890, believed that the periventricular grey substance of the third ventricle, the neighbouring portions of the aqueduct and the grey matter of the bottom of the 4th ventricle were the regulating centres for sleep. von ECONOMO, in 1916, concluded after studying the pathology of encephalitis lethargica that the

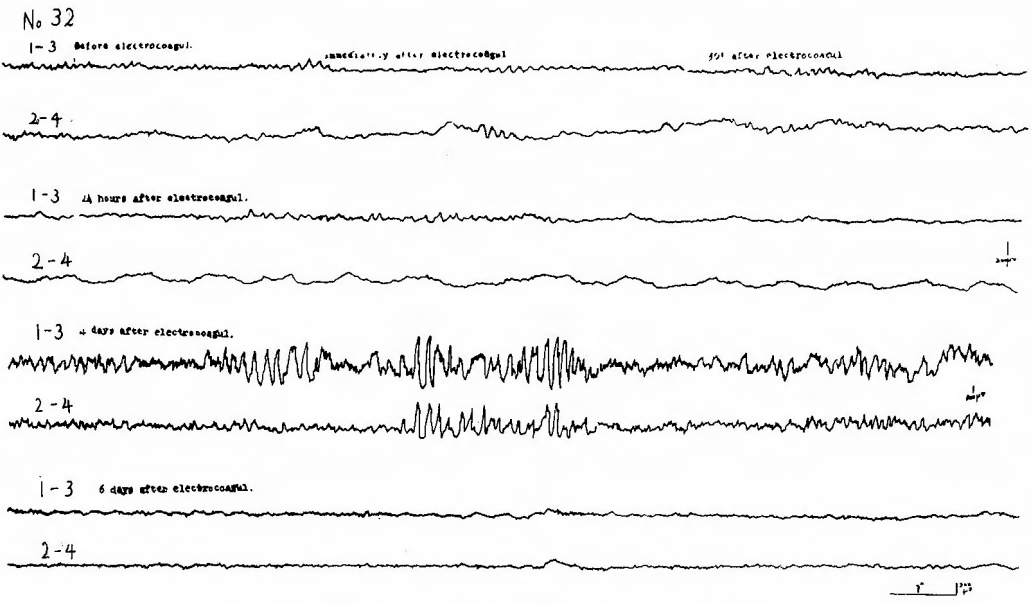

Fig. 19 The recording of EEG in cat No. 32

transitional portions from the subthalamus to the midbrain were the regulating centre for sleep. Following his work many investigators searched for the centres for arousal and sleep in the transitional portions from the diencephalon to the mesencephalon clinically, pathologically and experimentally. Since the work on the ascending reticular activating system by MAGOUN and his associates in 1952, a large amount of data has been accumulated concerning the function of the central cephalic portion of the brain stem in animals. MAGOUN confirmed experimentally that the interruption of the brain stem reticular system induced changes in the EEG like those seen in sleep and stimulation of the reticular system induced arousal behavior. This was a considerable contribution to an understanding of the mechanism regulating consciousness.

In the "coma puncture" experiments carried out in our laboratory over the past 14 years it has become increasingly clear that the central grey matter of the midbrain between the oculomotor and trochlear nuclei can sometimes function like a "switch of consciousness". In the present experiments, electrocoagulation by means of electric current of high frequencies destroys this portion in the main. However, judging from the stimulating symptoms which follow coagulation, such as, rigidity induced by weak current or clonic spasm of the whole body by strong current, or the moderate to extreme dilatation of the pupils during the periods of coagulation, or the mewing and crying (seen in some cases) just at the onset of current flow, it seems to be possible that the stimulating effects of electrocoagulation is more evident than the destroying effect during current flow. Considering from this the exhaustion after excitation or the functional disturbance due to abnormal excitation (like a sort of after-discharge) may be responsible for the temporary coma induced immediately after coagulation. (Unfortunately, in all comatose cases recording of

the EEG at the time of coma immediately after coagulation could not be done except in a comatose case due to subarachnoid bleeding.) The fact that no animals fell into coma when stimulating effects existing during and immediately after coagulation disappeared and the local destroying effects, that is, the local functional disruption appeared, would suggest that local partial functional disruption in the midbrain alone did not cause coma. In 5 of the 6 animals which became comatose, pathological examination revealed destruction of the central grey matter or both the central grey matter and the reticular formation. In the 6th comatose cat it seems likely that coma occurred secondarily to basal hemorrage. This would indicate that experimental coma defined above as the unresponsiveness to all external (especially nociceptive) stimuli is in most cases associated with abnormal stimulation of the central grey matter in the region extending from the oculomotor nucleus to the trochlear nucleus.

However, as has also been shown by other workers in our laboratory all injuries of this portion of the brain do not always induce coma. Therefore it seems that some secondary change rather than mere abnormal stimulation is necessary in order to induce coma. We are forced to the conclusion that the most reasonable explanation for coma is to assume a sort of seizure discharge arising and spreading over the entire midbrain adequately from the area of electrocoagulation.

It was very difficult to induce prolonged coma purposed primarily. However, when a large amount of the central grey matter was destroyed, the spontaneous movement and mewing were absent and the animal had anorexia. The animal was seen either sitting down apathetically oblivious to the ordinary environmental stimuli with the postural reflex still functioning or lying motionless on its side hanging its head down with no postural reflex. This occurrence is similar to the "simulating coma in man" delineated by MAGOUN. In this state the animal appeared as if dead except for the fact it was breathing. It was however not comatose according to our criteria because the noci-reflex was retained. At this point we cannot decide with certainty which takes the responsibility for this behavior between (i) the disturbance of consciousness, and (ii) extreme general exhaustion or a sort of exhaustive break down of all sympathetic nervous system. In this simulating comatose behavior of experimental animals, there was greater or less change in relation to greater or less degree of destruction. Whether or not coma (absence of noci-reflexes) was induced immediately after coagulation made no difference in this change. The greater the degree of destruction the less chance for the animal to recover destroyed vital function and the fewer postoperative survivals.

On the other hand when the destruction was slight, the cat became excited and mewed frequently, occasionlly snarling and raging on the Ist postoperative day. On the following day it became inert and apathetical to environmental stimuli except for mewing and did not show any interest in food or water. These behavioral abnormalities recovered gradually in 3 or 4 days and appetite, spontaneous movement and interest in environment reappeared. When the reticular formation was destroyed, if the destruction was large, the cat lay on its side hanging its

head down on the floor, with no postural reflex and no mewing or spontaneous movement except an occasional stepping movement. The appetite was lost immediately after electrocoagulation. If, on the other hand, the destruction was small, almost all the cats were active and walked ordinarily, mewed frequently and raged wildly. But the noci-reflexes were held in every case to the end and coma according to our criteria was never seen. That is, the behavioral difference between the large destruction of the central grey and that of the reticular formation was not seen except the occasional absence of noci-reflexes following operation was induced (in the former) or not (in the latter). When with reoperation 7 to 8 days after initial operation further destruction was added to the central grey matter, the reticular formation or other areas there was no difference made in behavior and the postoperative behavior was similar to that immediately prior to the 2nd coagulation.

Shinozaki, in 1937, reported that electrocoagulation of the periaqueductal tissue caused some disturbance of consciousness if the destruction was extensive but did not alter the state of consciousness if the destruction was small in amount or situated ventrally. In the present experiment and other experiments in our laboratory, i. e. local nicotine injection or local application of electronarcosis, the ventral portion of the central grey matter seemed more important than the other portions.

Bailey and Davis experimented with localized electrolytic lesions of the periaqueductal grey matter in cats (1942) and monkeys (1945). The behavior of these animals resembled strikingly the syndrome seen in human patients after lesions in the brain stem described by Bailey and etc. as "arrest of consciousness", and by Cairns and his coworkers as "akinetic mutism". It was similar to our result. But this work did not report EEG change or disappearance of noci-reflexes which might have been seen immediately after operation.

Lindsley, Schreiner, Knowles and Magoun, in 1950, in cats, and French and Magoun, in 1952, in monkeys, produced the chronic destructive lesions of the central cephalic brain stem and outlined clearly in cats the behavior pattern following injury of the midbrain tegmentum (chronic somnolence and hypokinesis, which we feel might correspond to the state of simulating coma seen in our animals). But caudal lesion on the periaqueductal grey matter in their experiments left the animal awake and alert from the first postoperative day with no greater disposition to sleep than that exhibited by a normal cat. In the only case of rostral lesion, the animal appeared asleep or drowsy from the first postoperative day. The animal exhibited little or no spontaneous activity and could not be aroused by afferent stimulation. In our experiments the caudal lesion produced the simulating coma too. The EEG in the Magoun's experiment showed large slow waves and spindle bursts and could not be activated when the animals were in somnolence or asleep. In the case of caudal lesions the EEG showed increased activity. On the contrary, in our experiments, the EEG did not show any characteristic form associated with the destruction of different mesencephalic areas. In these lesions made by Magoun and etc. of the reticular formation and central grey matter, it seems that neither coma

according to our criteria nor the flattening of the EEG tracings seen in our experiments was produced. In the experiments of MAGOUN and his co-workers the reticular formation was destroyed very largely and bilaterally. Localized destruction of one side such as we have done was not reported. In our experiments when occasionally a large amount of the reticular formation was destroyed although unilaterally, we observed hypersomnolence and hypokinesis or akinesis. But we did not trace the large slow waves seen in the EEG in the experiments of MAGOUN.

BAILEY and DAVIS, in 1942, described an interesting experiment, "the syndrome of obstinate progression in the cat". When the nucleus interpeduncularis was destroyed the cats in all cases began to progress obstinately forward making a peculiar low cry and never turned aside from any obstacle. This behavior continued as long as the animals survived, usually about 3 days. In our cat No. 27, the nucleus interpeduncularis and its neighbouring structures were destroyed, and during the week it survived, it did not show these peculiar behavioral changes.

SUMMARY

1) With the intention of producing prolonged coma (absence of noci-reflexes) experimental lesions were made in several portions of the midbrain in 52 cats.

2) In 4 cases, prolonged coma, lasting half an hour or more, developed immediately after operation and was in each case seen to be associated with electrocoagulation of the central grey matter, coagulation of both the central grey matter and the reticular formation, or coagulation of the crus of the cerebrum. However, electrocoagulation of all these parts described above did not always cause prolonged coma. On the contrary, prolonged coma occurred only in a few cases.

3) In most cases the appearance of the cats with the destruction of a large amount of the central grey matter resembled the behavior pattern called "arrest of consciousness" with noci-reflexes retained. Unfortunately, it is impossible to decide whether such behavior is due to a disturbance of consciousness per se or due to exhaustive inactivity. In the animals in which coma did not occur immediately following electrocoagulation, the course over the period of survival was similar to the prolonged course in those animals which did develop coma (absence of noci-reflexes) immediately, if the location and amount of coagulation were similar.

4) The behavioral difference between the large destruction of the central grey and that of the reticular formation was not seen except the occasional lack of noci-reflexes following operation was induced (in the former) or not (in the latter).

5) The EEG did not show any characteristic pattern associated with the destruction of different areas of the brain stem. In many cases, the EEG became flat immediately after electrocoagulation and in a short time moderate voltage slow waves appeared followed in 2 to 3 minutes by spindle bursts. In some cases low voltage fast waves continued as before operation and shortly after injury spindle bursts appeared. In other cases these fast waves slowed down and a short time later spindle bursts appeared as well. In all cases spindle bursts appeared 2 or 3 minutes after electrocoagulation and there was a tendency to synchronization. The

EEG recovered the preoperative low voltage fast waves from 5 to 8 days after surgery, but showed a tendency to flattening again little by little before death.

6) These experiments show that the central grey matter may be especially concerned with consciousness and it also seems that coma occurs as a result of abnormal excitement associated with the excessive stimulation due to coagulation. However, a similar amount of stimulation (a similar amount of electrocoagulation) does not always cause coma. Actually, coma appears to depend on some other secondary change. For example, the most reasonable explanation might be to assume a sort of seizure discharge originating at the site of the damaged mesencephalon and causing a widespread loss of function as it spreads over the midbrain.

References

I) Araki: Diencephalon and Disturbance of Consciousness. Saishinigaku, **8**, 41, 1953.*
2) Araki: Cerebral Trauma and Disturbance of Conscionsness. Sinryo, **9**, 1, 1956.*
3) Araki: Disturbance of Consciousness due to Head Injury, The VIIth Anual Meeting of the Japan EEG Society Symposia & Proceed. 1957. 4) Araki, C., Sakata, K. and Kuroki, T.: Pontine or "Reticular" Epilepsy, Report of a Case, EEG Clin. Neurophisiol. Journal, **8**, 4. 1956. 5)Araki, C., Taketomo, T. and Toda, T.: Coma puncture. Acta Sch. Med. Univ. Kioto, **27**, 205, 1949.* 6) Araki, C., Sakata, K. and Matsunaga, M.: Recruiting Response-Like EEG Changes Induced with Extrathalamic Stimulation of Cat. Acta Scholae Med Univers. Kioto Jap., **32**, 32-51, 1956. 7) Asai, S.: Electronarcosis by Direct Stimulation of the Brain Stem. Arch. Jap. Chir., **27**, 1, 1958.
8) Bailey, P. and Davis, E. W.: Effects of Lesions of the Periaqueductal Grey Matter in the Cat. Proceedings of the Society for Experimental Biol. & Medicine, **51**, 305, 1943.
9) Bailey, P. and Davis, E. W.: Effects of Lesions of the Periaqueductal Grey Matter in Cats and Monkeys. Abst. Arch. Neurol. & Psychiat., **53**, (4), 325, 1945. 10) Bailey, P. and Davis, E. W.: "The Syndrome of Obstinate Progression in the Cat" Proc. of the Society for Experimental Biol. and Medicine, **51**, 307, 1942. 11) Bernhaut, M., Gellhorn, E. and Raumussen, A. T.: Experimental Contributions to Problem of Consciousness. Journal Neurophisiolog., **16**, 21, 1953. 12) Davison, C. and Demuth, E.: Disturbances in Sleep Mechanism: A Clinico-Pathologic Study. IV. Lesions at the Mesencephalometencephalic Level. **53**, (1), 126, 1945. 13) French, J. D.: Brain Lesions Associated with Prolonged Unconsciousness. Arch. Neurol. Psychiat., Chicago, **68**, 727, 1952. 14) French, J. D. and Magoun, H. W.: Effects of Chronic Lesions in Central Cephalic Brain Stem of Monkeys. Arch. Neurol. Psychiat., Chicago, **68**, 591, 1952.
15) French, J. D., Verzeano, M. and Magoun H. W.: An Extralemniscal Sensory System in the Brain. Arch. Neurol. Psychiat., Chicago, **69**, 505, 1953. 16) Gerard, R. W., Machall, W. H. and Saul, L. J.. Electrical Activity of the Cat's Brain. Arch. Neurol. and Psychiat., **36**: 675, 1936. 17) Ishii, S.: Coma Puncture (Monograph). Kyoto, 1944.* 18) Jasper, H. H. and Cosimo Ajmone-Marsan: A Stereotaxic Atlas of the Diencephalon of the Cat. Montreal Neurological Institute of Mc Gill University. 19) Lindsley, D. B., Schreiner, L. H., Knowles, W. B. and Magoun, H. W.: Behavioral and EEG Changes Following Chronic Brain Stem Lesions in the Cat. Electroencephalog. & Clin. Neurophisiolog., **2**: 483, 1950.
20) Lindsley, D. B., Bowden, J. W. and Magoun, H. W.: Effects upon the EEG of Acute Injury to the Brain Stem Activating System. Electroencephalog. and Clin. Neurophisiol., **1**, 475, 1949. 21) Magoun, H. W.: The Ascending Reticular Activating System. Research Publications, Associations for Research in Nervous and Mental Diseases, XXX, 480, 1952.
22) Matsunaga, M.: Experimental Studies on Coma Induced by Stimulation of Various Parts of the Brain in Cat. Being prepared for publication. 23) Mauthner, L.: Zur Pathologie und Physiologie des Schlafes. Wien Klin. Wchnschr., **3**, 445, 1890. 24) Moriyasu, H.: To be published shortly. 25) Starzl, T. E., Taylor C. W. and Magoun, H. W.: Ascending Conduction in Reticular Activating System, with Special Reference to the Diencephalon. Journal Neurophisiolog., **14**, 461, 1950. 26) Yabuno, S.: Coma Puncture by Means of Nicotinization. Acta Scholae Med. Univers. Kioto Jap., **32**,

32-51, 1954. 27) Winkler, C. and Potter, A.: An Anatomical Guide to Experimental Researches on the Cat's Brain. Amsterdam, W. Verluys.
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和文抄録

中脳焼灼破壊後の急性並に慢性意識障碍

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私達は，成熟猫の中脳各所を，高周波電流によつて焼灼破壊する実験を行い，(i)成るべく長時間の焼灼直後昏睡（侵害反射消失），及びそれに続く慢性反応遅鈍状態を作り，(ii) その各時期に於ける，脳波上の変化を追求し，(iii)併せて，中脳中心灰白質と，中脳の被蓋網様織との焼灼効果の差を調べた．その結果，焼灼直後の昏睡は，中脳中心灰白質より，而もその破壊によつてではなく，異常刺戟によつて起るものなること及びその後の慢性反応遅鈍状態（これは破壊性機能脱落による）は，直後昏睡の発現の有無とは無関係に，而も中心灰白質及び網様織の何れからでも出現することを認めた．

即ち，中心灰白質を大きく破壊すると，動物は生存期間中(1～7日)，じつと坐つているか，横に倒れて合目的的に動かず，鳴かず，食慾を示さない．(Bailey and Davis の実験的 akinetic mutism に相当する．) 破壊の程度が大きい程，生存期間が短いが，死亡する迄この状態が続いている．破壊が小さければ間もなく正常に戻るが，焼灼後暫らくは，興奮乃至怒りの状態を示す．中脳被蓋網様織の破壊でも，略同様の行動上の慢性変化を示したが，焼灼直後の侵害反射の消失のみは見られなかつた．

脳波上は，直後昏睡の出現の有無に拘らず，焼灼と共に先づ平坦化を示し，次いで紡錘波の出現することが多かつた．低電位速波，或いは中電位徐波の現れたこともあつたが，何れの場合でも，一定時間後反応遅鈍状態に入ると，紡錘波が必ず現れ，又外来刺戟によつて desynchronize されない傾向を示した．そして，焼灼部位が中心灰白質でも，網様織でも，その間に差異を示さなかつた．

要之，焼灼直後の昏睡に対しては，中脳中心灰白質が最も関係が深いと思われ，而もこの昏睡は，破壊による機能脱落によるものではなく，異常興奮即ち，発作放電の様なものが，中脳の焼灼された部位から起り中脳全体に拡がつて，その全般的機能喪失を起すことによるとでも仮定したら良いと思われる．他方その後の慢性反応遅鈍状態の方は，akinetic mutism に相当するものと思われるが，之は中脳の中心灰白質からでも，網様織からでも起り，局所破壊による機能脱落症状と解される．