

EXPERIMENTAL STUDIES ON COMA DUE TO HEAD INJURY

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Introduction

In the present experiments in order to study the mechanism of coma in the brain injury, the localized mechanical violence was inflicted selectively on the various parts of brain especially the brain stem. This was done to determine in what portions the injury produced coma. Furthermore, since changes in the cerebral electrical activity in coma cases have been increasingly discussed in recent years, the relationship between coma and EEG changes was investigated in this experiment.

Experiment I. (Coma due to a penetrating shoot)

At the start, we tried to shock the midbrain with a small iron fragment which was inserted into the midbrain and vibrated at 60 cycles between two electromagnets. But this method was revealed to be less effective in inducing coma than the sudden external violence, e. g. the sudden accidental puncture by an operating instrument at the moment when the cat raged during the operation. DENNY-BROWN, WALKER and others have caused successfully the experimental concussion, contusion and laceration by means of applying various types of blows upon the skull or upon the intact dura mater. This suggests that the impact is more effective than the vibration in eliciting coma.

Methods

A mature cat's head was fixed and his skull and dura mater were bilaterally removed in the temporal region for about 2.0×2.0 cm to allow an adequate exposure. The exposed brain was penetrated transversely and horizontally with a special impact apparatus constructed for this experiment modeled after an air-rifle (Fig. 1). For the course of 1~3 hours after the impact, alterations in the nociceptive reflexes and in the behavior were observed. All cases were operated on under the ether anesthesia and the experiments were started at least $\frac{1}{2}$ hour after obvious recovery of the consciousness. After each experiment, the cat's brain was examined at autopsy and preserved in formalin-solution for several days. The penetrating tract was determined by both midsagittal section and transverse section, and the relation between its site and the occurrence of coma was investigated.

The bullet was a small lead ball with a diameter of 2.5 mm. The shooting power at a distance of 15 cm from the muzzle of the rifle was approximately 7900 erg (Fig. 2). This value corresponded to the power which allowed penetration

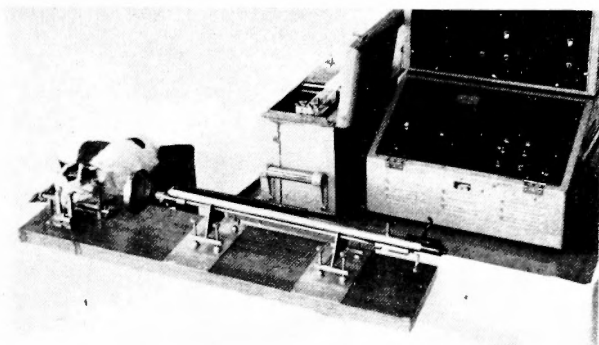


Fig. 1 Illustrates the cat's head-holder, impactor (air-rifle) and EEG-recorder. The head-holder was designed to hold the cat's head at his external auditory canals, the lower edges of the orbits and the lower edges of the maxilla, in similar way to the HORSLEY-CLARKE stereotaxic instrument. This holder allows penetration from the side. The impactor (air-rifle) was placed on the same board on which the head-holder was fastened. The calibre of rifle was 2.8mm in diameter. Shooting power could be changed to same degree according to the air-pressure. There was a card-board baffle in front of the rifle muzzle, so that the direct effect of compressed gasses on the brain was blocked. The rifle was always aimed by the adjusting calibration apparatus.

through the ipsilateral skull and brain, the bullet stopping short of the contralateral skull, when a cat of 1.5 kg weight whose extracranial soft tissue was removed (without resection of bone) was shot through the skull.

Cortical electrical activity was picked up with four needle-shaped electrodes driven into the skull until their tips rested upon the dura mater overlying the anterior and posterior parts of each hemisphere. Fronto-occipital bipolar records on both hemispheres were taken with a two-channel inkwriting SANEI-EEG-recorder.

Criteria for coma

When a cat ceased his spontaneous movement and mewing and completely lost the nociceptive reflexes and postural reflexes, the state of the animal was judged to be coma. But it was not infrequently difficult to distinguish the loss of postural reflexes from the simple physical exhaustion; so that the postural reflexes were sometimes useless as criteria. As the loss of the noci-reflexes lasted approximately for only 1 minute in most cases, we did not have enough time to examine many of the noci-reflexes; but we could test only, the pinna, pharyngeal, corneal reflexes and the avoidance reaction to painful stimuli on the foot pad. In the experiments of shooting through the hypothalamus the temporal muscles, masseter muscles and zygomatic arches had to be removed in a preliminary operation, also the branches of the facial nerve running over the surface of these

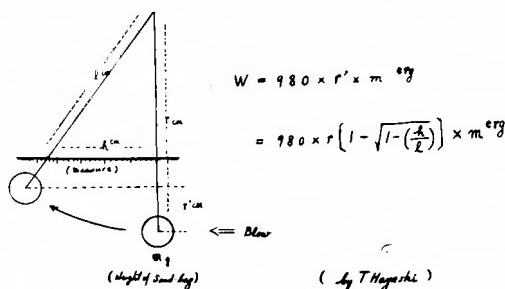


Fig. 2 Shooting power was calculated according to this formula by means of shooting a sand-bag hung by a thread at the same distance and power as in the experiment. h : measured distance of movement of the thread in a horizontal plane at impact. (by T. HAYASHI)

muscles were usually interrupted. As a result the corneal and pharyngeal reflexes became masked, so instead of these, the avoidance reactions to stimuli to the tip of the nose and the sneezing reaction to naso-septal stimuli were tested.

The cases in which the cats ceased their spontaneous movement and mewing, while the loss of the noci-reflexes was not complete, or those cases in which some of the noci-reflexes were retained, were regarded as semicoma cases. Cases in which spontaneous movement or mewing did not cease, or cases in which the noci-reflexes were not weakened, were included in the non-coma cases.

Results

1) Neurological manifestations associated with coma.

Coma cases showed various neurological manifestations in addition to the cessation of spontaneous movement and the loss of the noci-reflexes.

a) Extremities. All coma cases and some non-coma cases (especially cases penetrated in the septal region) were accompanied by the instantaneous spastic extension of the extremities at the moment of impact. This was called "tetanic phenomena" by WALKER. In some cats the relaxation of limbs soon followed. This was noted when the animal was penetrated on the rostral portion of the mesencephalic central grey matter. In other cats there was a residual rigidity persisting for a while which was more conspicuous in the forelegs. The electromyogram

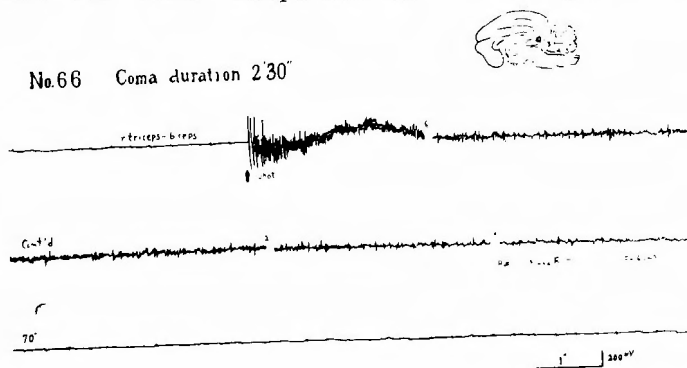


Fig. 3 Electromyogram recorded with bipolar leads from the m. biceps and the m. triceps on the right foreleg. It showed the remarkable interference voltages.

revealed the remarkable interference voltages on such legs (Fig. 3).

b) Respiration. At the moment of impact the cat ceased his respiration for a few seconds. This phenomenon was more remarkable in a cat which had the intense spastic extension of the extremities. Then shallow respiration began, followed by gradual recovery. The electromyogram on the respiratory muscle also revealed the remarkable interference voltages (Fig. 4) (Fig. 5).

c) Patellar reflex. This was examined in one coma case by means of JOHNSON's electromagnetic hammer and kimograph. Remarkable diminution of the tendon jerk reflex continued for a shorter period than the loss of the noci-reflexes (Fig. 6).

d) Blood pressure. It rose in the initial period and descended below the pre-shoot level in the succeeding period, and then it returned gradually to the

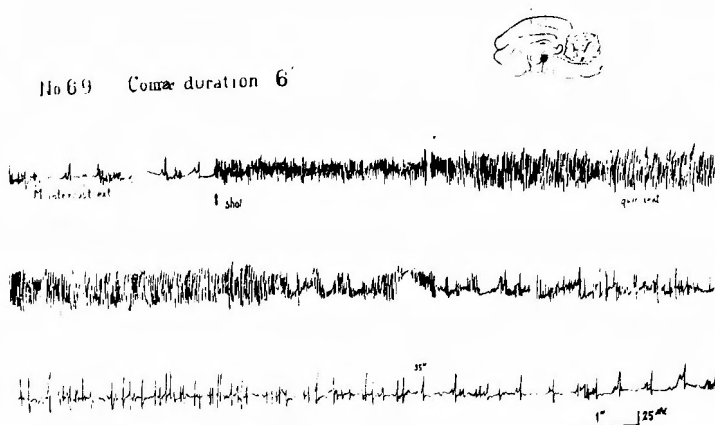


Fig. 4 Electromyogram recorded bipolarly from the *m. intercostalis externa* after exposure of the intercostal muscles. It showed also the remarkable interference voltages.

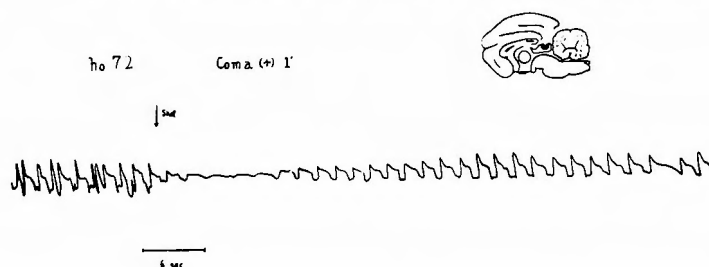


Fig. 5 Kimogram of respiratory change made with a cannula inserted into the trachea. Respiration ceased for about 10 seconds.

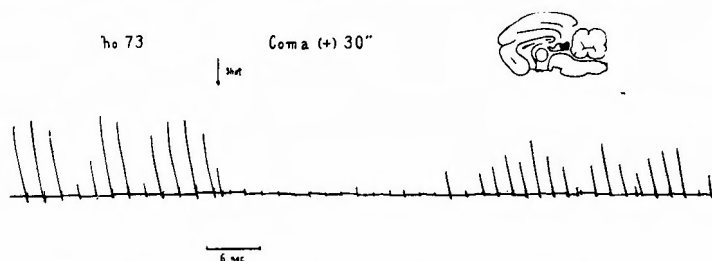


Fig. 6 Kimogram of the patellar reflex on the left hind leg. After the thigh-bone was fixed, the patellar tendon was tapped with JOHNSON'S electromagnetic hammer on every 2 seconds, and movement of the leg was recorded on the kimograph. The reflex diminished markedly for about 20 seconds.

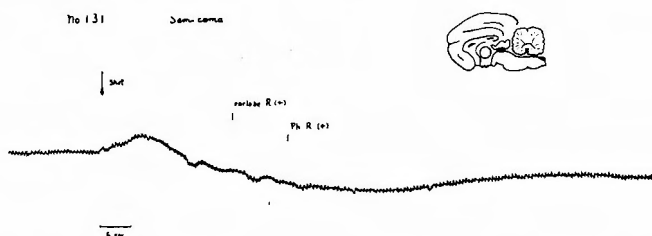


Fig. 7 Kimogram of the blood-pressure taken through a cannula inserted into the left carotid artery. Pressure rose initially, descended after that and then returned to the pre-shoot level. (by T. HAYASHI)

pre-shoot level. This was similar to HAYASHI's experiments in our laboratory in which the blow was given to the whole brain (Fig. 7).

e) Pupils. They dilated initially and constricted gradually in the succeeding period. At the penetration of the midbrain the pupils dilated immediately after the shoot. In the penetration of the rostral part of the hypothalamus or the septum pellucidum the pupils dilated gradually following the shoot.

2) Distribution of areas of coma-inducing shoots (Fig. 8).

Except for the preliminary experiments and the control experiments, 18 experiments out of 38 performed in 32 cats showed coma or semicoma. Distribution of bullet-marks on the mid-sagittal plane is shown in Fig. 8. We see that, coma and semicoma were present only in the penetration of the midbrain or hypothalamus. The most prolonged coma was seen in cases of penetration of the transitional portion from the aqueductus SYLVII to the third ventricle, especially on the rostral tip of mesencephalic central grey matter and through the base of crus cerebri. In the last

case rigidity of the extremities continued for a long time. The penetration of the hypothalamus showed either coma or semicoma. The penetration of the dorsocaudal part of the hypothalamus tended to result in coma.

In the midbrain, the penetration of the central grey matter showed semicoma while the injury of the corpora quadrigemina showed coma almost constantly. A cat penetrated at the reticular formation between the central grey matter and the crus cerebri at the level of the colliculus superior showed hypersensitive nocireflexes, though spontaneous movement ceased. This was regarded as no-coma according to our criteria. The penetration of the septum pellucidum, the gyrus cinguli and the dorsal part of thalamus did not show coma. Injuries of the septal region were apt to cause rigidity of the extremities and some of them were regarded as tonic convulsions.

It was not possible because of the eye bulbs to apply these shoots to the ventral part of the frontal lobes. Also the pons and the medulla oblongata were difficult to injure because they were hidden between the bilateral temporal

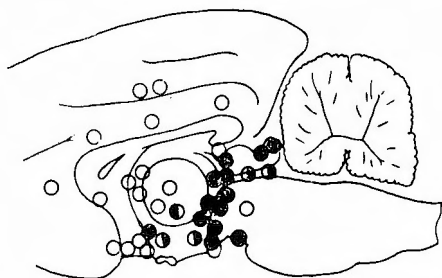


Fig. 8 Marks showing centers of shoot tracks. Actually destroyed areas were larger than these marks. A black circle indicates the center of a coma shoot. A double circle indicates the center of a more prolonged coma shoot in which unresponsiveness lasted for longer than 5 minutes.

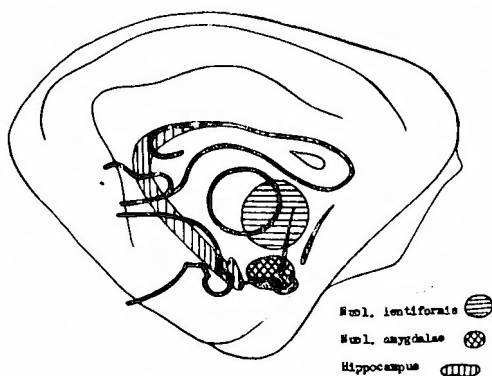


Fig. 9 Pes and digitationes hippocampi, nucleus amygdalae and nucleus lentiformis projected to the mid-sagittal plane (mid-sagittal reconstruction).

pyramids. Many of the coma cases with the brain stem penetration were penetrated simultaneously through their hippocampus, gyrus hippocampi or nucleus amygdalae, or neighboring structures inside of the temporal lobes (Fig. 9). Some control experiments in this regard will be described later.

3) Representative cases of injury to each region and the changes of cerebral electrical activity accompanying these injuries.

a) Mesencephalon

Cat 66 (Fig. 10) was penetrated at the colliculus inferior and caudoventral edges of the occipital lobes at a considerable distance from the pes hippocampi, so that the bilateral pes hippocampi were intact. Coma was produced.

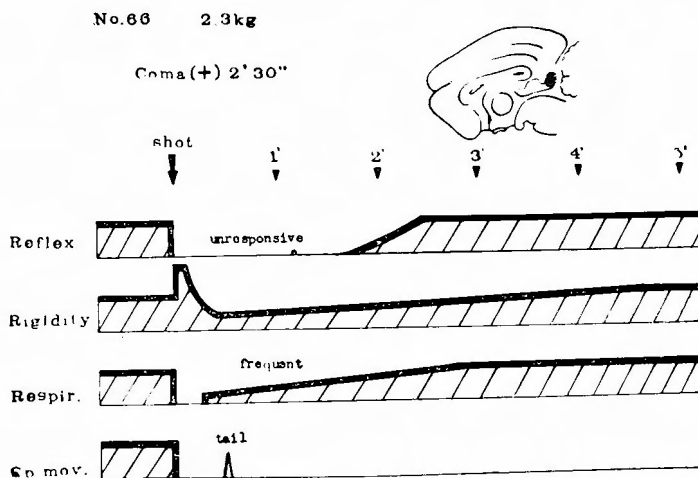


Fig. 10 Various reactions following the shoot are illustrated schematically. The lines show the data measured not precisely with an instrument, but merely by guess. 1st line: nociceptive reflexes. 2nd line: muscle tension. 3rd line: depth of respiration. 4th line: spontaneous movement.

Before the shoot the cat moved actively and his noci-reflexes were brisk. At the moment of shoot, he had the instantaneous spastic extension of his extremities. He ceased his respiration, mewling and spontaneous movement. All noci-reflexes vanished. In about 10" (after the shoot) superficial and frequent respiration began and the muscle tension was reduced but did not relax completely. The pupils were mydriatic. In about 40", he moved his tail once, but he was quiescent thereafter. In about 1' 40" the corneal, pinna and pharyngeal reflexes began to return in this order. In about 2' 30" the cat avoided painful stimuli on his foot pad, but he did not rage. At 2° 30' he kept his eyelids closed just as if sleeping and was quiet without movement. When painful stimuli were applied to his body, he awoke and moved for a while, but soon fell into sleep. At that time, the noci-reflexes and respiration were almost normal.

Cat 64 (surface EEG) (Fig. 11); the bullet penetrated through the rostral part of colliculus superior, scraping the geniculus lateralis and passing through the pes hippocampi. Coma was produced.

For the initial 4" the EEG showed low voltage fast waves and then it was flattened. In about 15" (after the shoot) it changed to high voltage slow waves of 2~3 per second.

Cat 74 (Fig. 12); the bullet penetrated the rostral tip of mesencephalic central grey matter, passing adjacent to the caudal edge of the pes hippocampi on one side, and in front of the pes hippocampi on the other side. There was very prolonged coma with unresponsive-

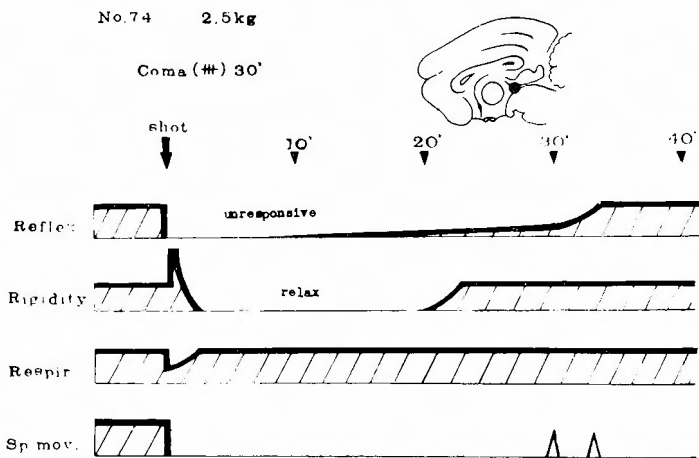
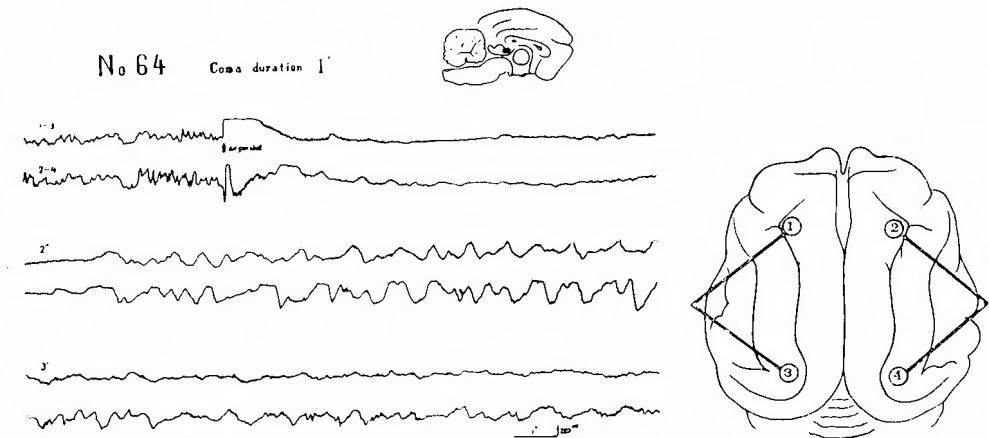


Fig. 12

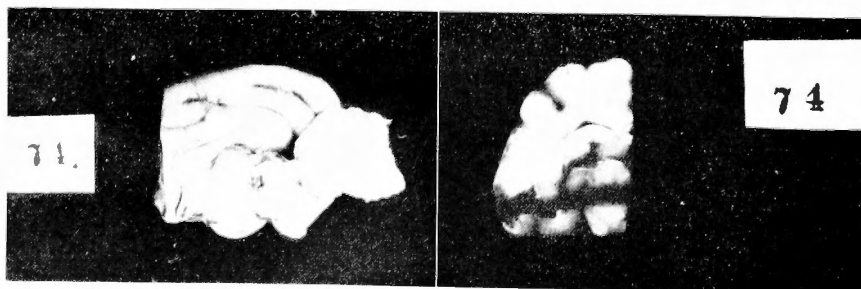


Fig. 13 Actual area of destruction in cat 74. Figure on the right shows a shoot track in a transverse section.

ness for 30'.

At the impact the instantaneous spastic extension was seen of the extremities which then became flaccid. The cat had trismus. Respiration was suppressed initially but later returned to almost normal. Noci-reflexes vanished completely except for the right corneal reflex which slightly remained. There was no spontaneous movement, and no mewing. At 25' (after the impact) the pharyngeal reflex reappeared. There were occasional deep respirations but generally respiration was steady. At 30' the pharyngeal reflex was normal. Though weak, the corneal and pinna reflex were also noted. At 1° 15' the cat raged, avoiding painful stimuli to his pad, but while he was left without stimulation he was quiet. Noci-reflexes were normal except for the left corneal reflex which was a little weak (Fig. 13).

The surface EEG was obtained in cat 74 (Fig. 14). Initially the pre-shoot pattern remained and at about 10" after the shoot a diminution of amplitude appeared. At about 2' the pattern was flattened markedly and the spindle bursts of 4~6 per second appeared overlapping rather regularly.

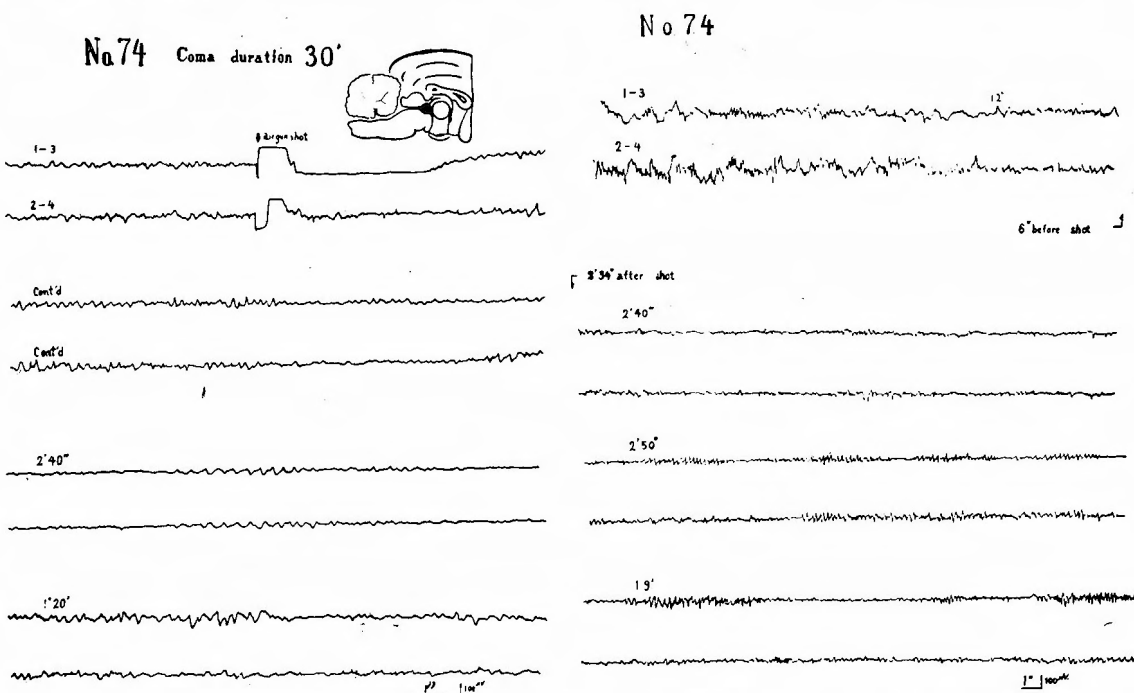


Fig. 14 The portions of the records taken at the speed of 3 cm per second were shown in the figure on the left and those at the speed of 1 cm per second were arranged in the figure on the right. In the right figure the moment of shoot is not shown in the figure. It is in the blank space between 1st pair and 2nd pair of recorded lines. "cont'd" means that the end of the upper pair continues to the beginning of the next pair without omitted interval.

Cat 84 (Fig. 15) was penetrated at the transitional portion from the midbrain to the hypothalamus, the pes hippocampi being destroyed. Coma resulted.

At the moment of impact he had the instantaneous spastic extension of his extremities with subsequent rigidity lasting for less than 1'. Noci-reflexes vanished for about 1'. Respiration ceased instantaneously but immediately it reappeared with the sluggish and superficial excursion. Gradually it recovered. Spontaneous movement ceased from the shot moment, but the cat moved his tail after 5' and raged when painful stimuli were given. At 15' after the shoot he began to move actively. At the moment of impact he once screamed loudly, but he did not

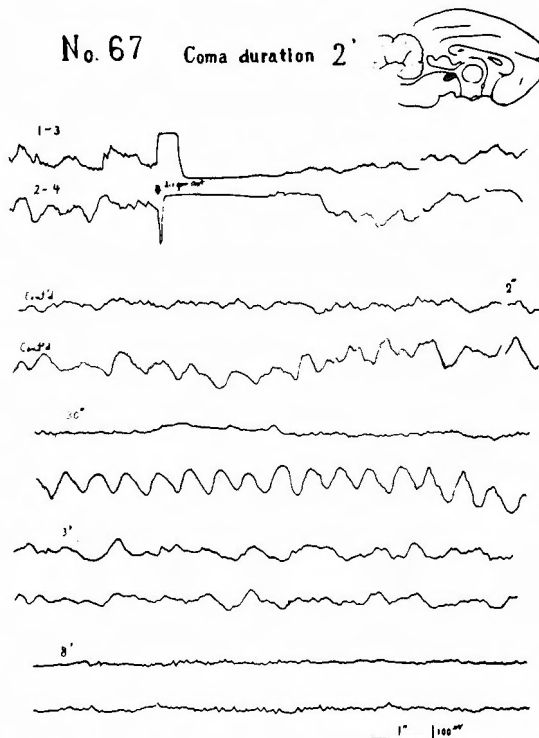
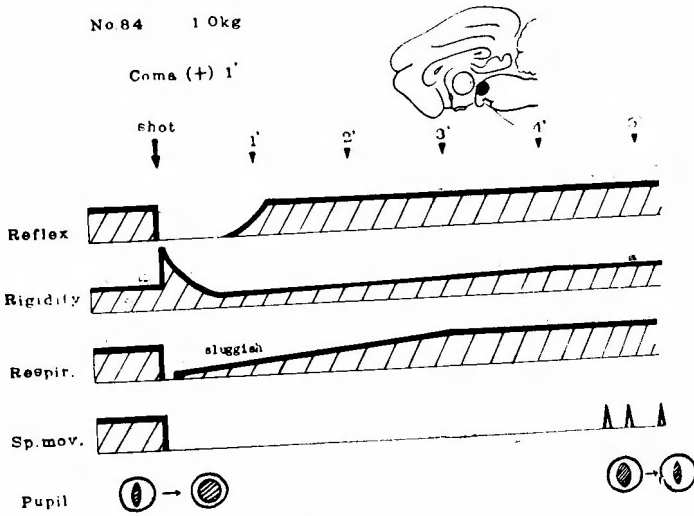


Fig. 16 Unresponsive till the 3rd pair of lines. The 4th pair is in the period of consciousness.

mew thereafter. The pupils dilated immediately after the shoot and returned to normal after 30'.

Cat 67 (Fig. 16) was penetrated on the ventral portion of the aqueductus SYLVII at the level of the oculomotor nucleus, and laterally through the pes hippocampi Coma resulted.

There were no flattened waves at least immediately after the impact. After transient

slow waves, a tendency towards flattening appeared in one channel, while high amplitude rhythmical waves were seen in the other channel. These could not be distinguished from artifacts. Subsequently the temporary slow waves were followed by flattening.

b) Hypothalamus

Cat 91 (Fig. 17) was penetrated through the dorsocaudal part of the hypothalamus, and the uncus gyri hippocampi. Coma resulted.

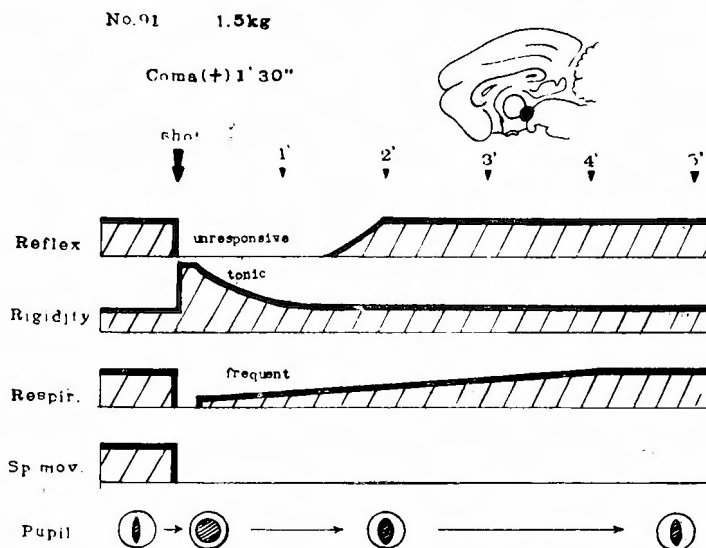


Fig. 17

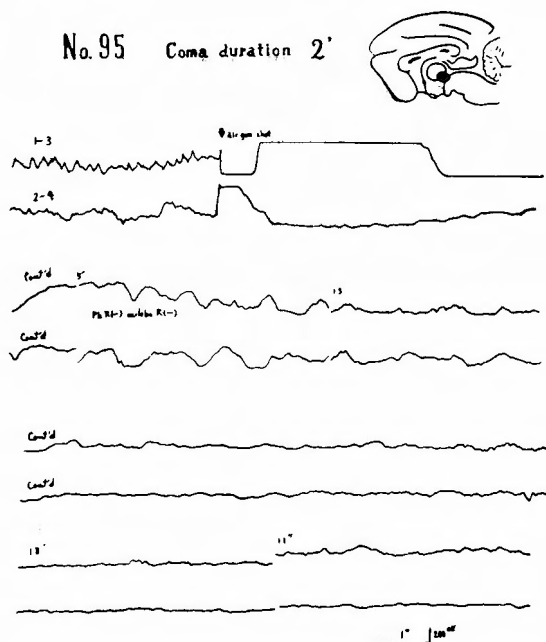


Fig. 18 Unresponsive till the 3rd pair of lines. The 4th pair is in the period of consciousness.

Rigidity of the four limbs continued for 1' 30" and did not completely relax after that. Initial cessation of respiration was followed by accelerated and superficial respiration. At 1'

20" after the shoot, for the first time the cat avoided painful stimuli. The pupils dilated immediately after the impact and returned to the normal condition in 5'. After that miosis developed. The pinna reflex reappeared at 1' 30". The corneal and pharyngeal reflex came out in 2'. Spontaneous movement could not be seen at all after the shoot.

Cat 95 (Fig. 18) was penetrated on the same portion as cat 91. Coma resulted.

A 6 per second pre-shot pattern disappeared and slow waves developed. At about 30" (after the impact) flattening occurred.

Cat 94 (Fig. 19) was penetrated through the hypothalamus between the level of the corpus mamillare and that of the chiasma opticum. Laterally the track passed adjacent to the pes hippocampi, and partially scraped the nucleus amygdalae. Semicoma resulted.

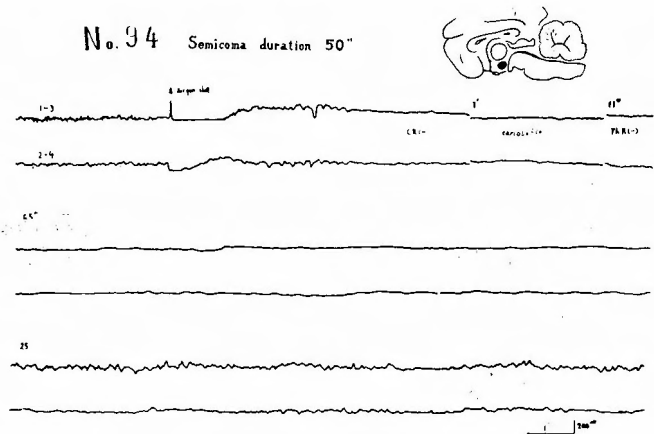


Fig. 19 The 2nd and 3rd pairs correspond to the period of consciousness.

A pre-shoot EEG pattern remained for about 5" after the shoot, and then EEG was flattened. 6 per second waves reappeared in about 25' after the shoot.

c) Thalamus

Cat 78 (Fig. 20) was penetrated through the central part of the massa intermedia and the nucleus lentiformis. No coma resulted.

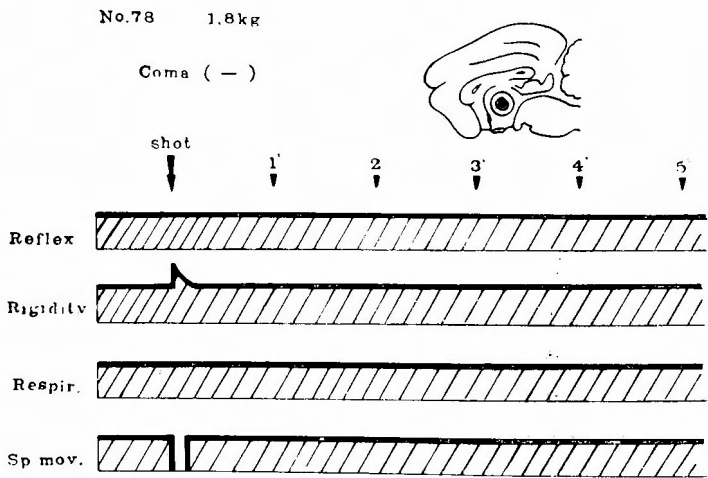


Fig. 20

Noci-reflexes did not vanish. Although he had the instantaneous spastic extension of his extremities, the momentary cessation of spontaneous movement was soon followed by active movement and mewing. Respiration was almost normal. The general behavior was somewhat sluggish in comparison with that before the experiment. No other noticeable change was present.

d) Septum pellucidum

Cat 90 (Fig. 21) was penetrated at a point rostral to the commissura anterior, and laterally at the rostral margins of nucleus amygdalae. No coma resulted.

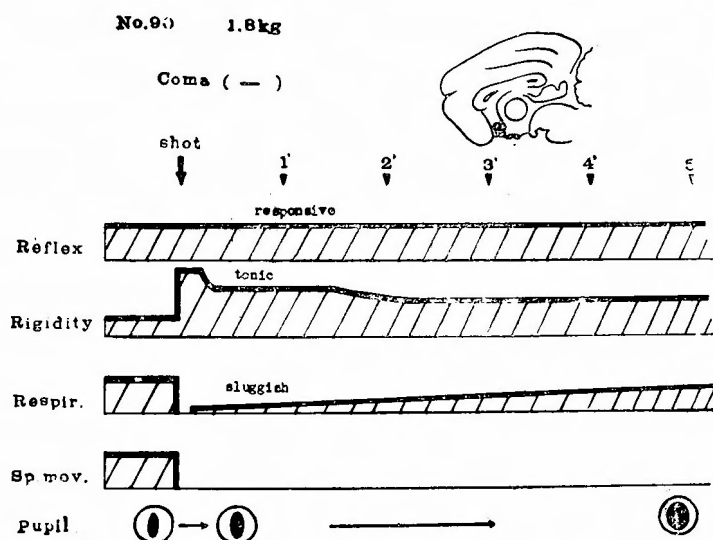


Fig. 21

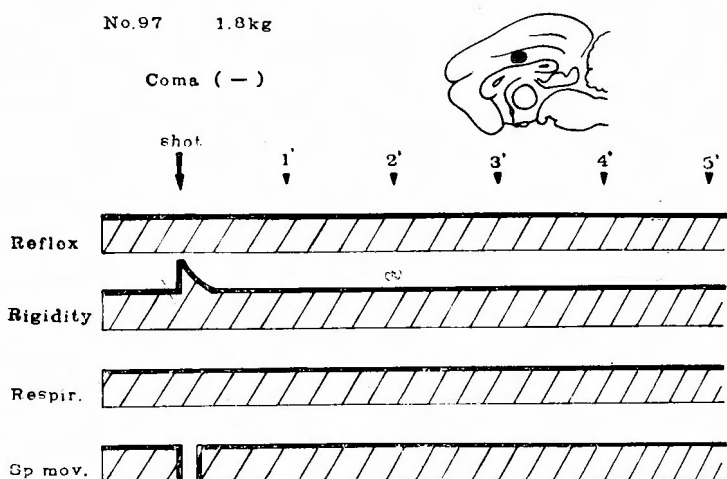


Fig. 22

The cat ceased his spontaneous movement and mewing but all noci-reflexes were retained. Tonic extension of the extremities remained for 2' following the shoot. Respiration, after momentary arrest, began again though superficial and sluggish. In about 8' after the shoot his spontaneous movements reappeared. The pupils dilated after a while, reached maximal mydriasis in 5' and then constricted again gradually.

e) Telencephalon

Cat 97 (Fig. 22) was penetrated at the gyrus fornicatus (gyrus cinguli in man). No coma resulted.

The cat ceased his spontaneous movement for a moment with slight spastic extension of his extremities, but soon he moved as actively as before the experiment. He had no change in his respiration and noci-reflexes.

Cat 70 (Fig. 23) was penetrated on the gyrus splenialis. No coma resulted.

Flattening of the EEG was more conspicuous than in the cases above and did not recover for a long time. Some EEG waves were present in the initial period.

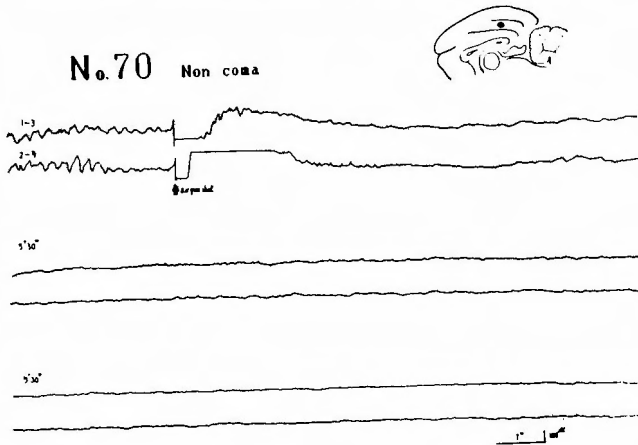


Fig. 23 Calibration corresponds to 100μ v. Therefore, the flattening of the EEG is most striking in all cases. (Calibration in the preceding case was 200μ v.)

In all cases, from the moment of shoot the cerebral tissue began to swell out of the bilateral bone defects. This swelling reached a peak in 15'' on an average. There was no tendency to shrink at least in the course of 1~3 hours. It should be regarded as an acute brain edema caused by the impact, because we did not see any large intracranial hematoma responsible for this swelling.

A characteristic feature of the EEGs in this stage was the flattening.

a) This tendency of flattening was most conspicuous in cases of the shoot through the telencephalon in which coma was not induced, and next apparent in cases of the penetration of the hypothalamus. In the midbrain cases in which coma was most easily induced, this tendency towards flattening was the least conspicuous and the pre-shoot EEG waves remained most frequently. The waves remaining were mainly the slow waves.

b) This flattening was not so striking immediately after the shoot. In this initial period, there were low voltage fast waves or the pre-shoot pattern and the marked flattening was seen in the following period. Considering the time it occurred, it might have been caused by the brain edema.

4) Control experiments

a) Shoot of 7900 ergs penetrating the gyrus cinguli of the cat whose temporal

bones were bilaterally removed did not induce coma as described above. The same strength of shoot penetrating the same portion in another cat, which was craniectomized only on the side of inshoot, also did not induce coma.

When the exposed skull without window was penetrated with 44600 ergs of shot, i. e. a little more than 5 times as powerful as an usual shoot, obvious coma was caused by a penetration of the same area. In the case, it seems that the violence of the impact affected not only the region along the track of penetration but also the whole brain.

b) In all penetrations in experiment I, the destruction of tissue was always accompanied by an expanding shock or impact. In order to see the effect of destruction without such an expanding impact, a steel needle of the same diameter as the bullet was inserted slowly with the hand transversely and horizontally. Coma was not induced by the stab in the transitional portion from the aqueductus SYLVII to the third ventricle, in the middle part of the colliculus superior and even in the transitional portion from the midbrain to the hypothalamus. Moreover, even when the destroyed areas were enlarged by several times repetition of stab, coma was not induced.

c) In order to examine if this coma which had occurred with the penetration of the brain stem might be the result of a concomitant temporal lobe injury, we did bilateral partial resection of temporal lobes, including the pes hippocampi, and then made a penetrating shoot through this temporal defect. Coma was induced. Autopsy revealed that the penetrating force passed through the dorsocaudal portion of the hypothalamus adjacent to the massa intermedia; nearly the same region as in cat 91 (Fig. 17).

Experiment II.

(Coma due to a localized shock to a restricted small region of the brain.)

From experiment I, we knew roughly the portions of the brain, destruction of which led an animal to coma. Now we attempted to inflict a less violent and more restricted impact on those portions of the brain by means of a machine described below in order to reveal more exactly which portions were most intimately related to coma caused by injury. In this experiment we could make a localized destruction of the pons and medulla oblongata, which was not done in experiment I for anatomical reasons.

Methods

We constructed a small needle-shaped shocking machine with an elastic spring for the special use of this experiment. The knife and its cover at the end of a FRANKÉ's blood lancet were taken off and replaced by a puncture needle (pipe) containing a steel stylet with a diameter of 0.8 mm. When the handle of the machine was pushed, the steel stylet within the needle was let project for 4 mm out of the end of the outside needle (pipe) by the action of an elastic spring. The top of the inside needle (stylet) was cut at a right angle to its long axis in order to make the impacting surface large, while the top of the outside needle (pipe)

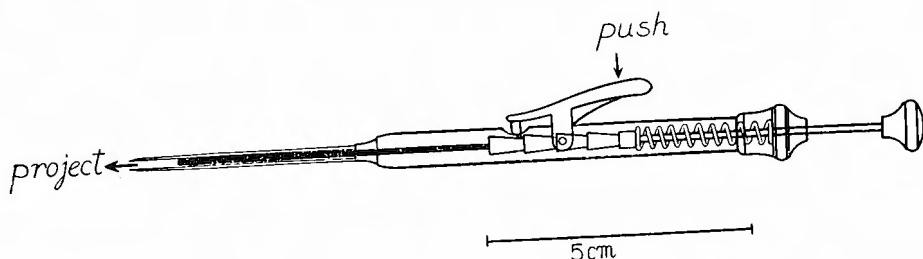


Fig. 24 Spring-shocking machine. The part of the machine to be inserted into the brain was coated with the paint for insulation. On one side of the tip of the outside needle, the steel was left uncoated for an area of 1×3 mm for the benefit of electrostimulation or direct-current coagulation after the experiment. In addition, a steel wire of 0.1 mm in diameter coated with the paint for insulation except for its tip was attached and fixed along the side of the outside needle. It was used as the other electrode in electrostimulation.

was made thinner towards the end for easier insertion (Fig. 24) (Fig 25).

A mature cat was fixed on a hammock and a HORSLEY-CLARKE stereotaxic instrument with this shocking machine fitted up was installed on his head. Under ether anesthesia the shocking machine was inserted into the brain through a small bone hole. About 30 minutes later, when the cat was fully awake, the machine was shot and a localized shock

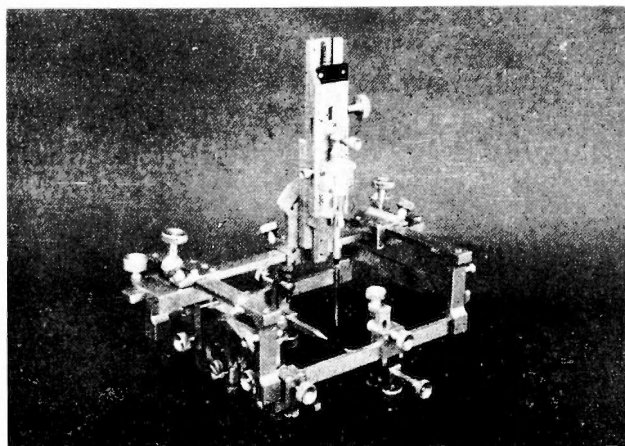


Fig. 25 Illustrating the spring-shocking machine fixed in position on the HORSLEY-CLARKE stereotaxic instrument.

was given to the various portions within the brain. EEG recordings were made with a fronto-occipital bipolar lead in one channel placed 2 mm laterally from the midline of the skull. After death of the cats, the brains were frozen or embedded in celloidin and sectioned. To confirm the shocked areas myelin sheath stain was done in all cases, and Nissl stain or hematoxylin-eosin stain on occasion.

Criteria for coma

These were essentially the same as in experiment I. However, as the unresponsive phase was too short to allow the examinations of all noci-reflexes, mostly the pinna reflex and occasionally the corneal reflex were examined repeatedly and the duration of loss of these reflexes was regarded as the duration of coma.

Results

1) Neurological manifestations in association with coma.

The manifestations are in general nearly the same as those in experiment I but less distinct. That is, the cat had a spastic extension of his extremities at

the moment of shock, ceased his spontaneous movement and mewing. Though in some cases there was a temporary acceleration or a short pause, there were usually less changes in respiration in comparison with the animals of experiment I. The loss of the noci-reflexes usually lasted only for 3~10 seconds and their recovery always preceded the reappearance of spontaneous movement. The instantaneous spastic extension of the extremities was present not only in coma cases but also in some non-coma cases.

2) Distribution of points of coma-inducing shock.

46 experiments were carried out on 23 cats. From one to three shocks were inflicted on different portions of a cat's brain. In these animals, coma and semi-coma were seen in shocks of 11 points distributed from the midbrain to the rostral part of the medulla oblongata. No coma case was seen in shocks of the telencephalon and diencephalon (Fig. 26).

Distribution of the locations of coma- or semicoma-causing shocks in the mid-brain occupied mainly the central grey matter, the nucleus interpeduncularis and raphae, and occasionally the reticular formation.

Shocked portions in the pons and medulla oblongata were located in the central one third and all coma-producing areas were limited to the rostral portion from the nucleus dorsalis nervi VIII.

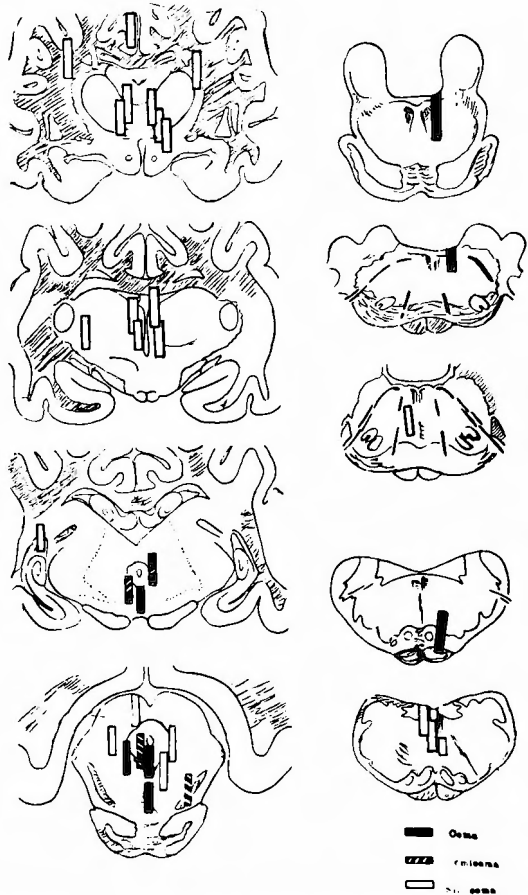


Fig. 26 Distribution of the areas shock to which caused coma (black mark) and semi-coma (stripe mark). Coma was not induced in those portions with white marks.



Fig. 27 Histological preparation of Nissl stain in cat 123 showing the real magnitude of destruction as an example in this experiment. Two arrows indicate the track of shooting. Shoot was supposed to have begun at upper arrow and reached to lower arrow.

3) Representative cases of coma shock in each region.

a) Telencephalon and diencephalon.

Noci-reflexes did not diminish nor vanish. The instantaneous spastic extension of the extremities was slight, or absent. In most cases spontaneous movement did not cease. There was no change of respiration. The portions hit by the shocking machine are indicated with the names of the existing nuclei, e. g.:

Thalamus: Nucleus reticularis, Nucl. reuniens, Nucl. anterior medialis,
Nucl. medialis dorsalis, Nucl. centralis medialis,
Nucl. centrum medianum, Nucl. centralis lateralis,
Nucl. interanteromedialis, Nucl. ventralis medialis,
Nucl. ventralis postero-lateralis, Nucl. paracentralis,
Lamina medullaris externa.

Hypothalamus: Area hypothalamica dorsalis, Hypothalamus posterior, Subthalamus.

Telencephalon: Capsula interna, Area amygdaloidea anterior, Gyrus cinguli, Hippocampus.

Anatomical guidance was obtained from HERBERT H. JASPER and COSIMO AJMON-MARSAN (1954)*

Cat 123 (3rd shoot). 2.0 kg male. No coma was produced (Fig. 27). Before the shoot he was actively mewling and moving. He had no spastic extension of his extremities at the moment of shoot. He had neither change in his noci-reflexes nor in his behavior. The shoot track extended from the medial portion of the thalamus, i. e. the nucleus centrum medianum and nucleus medialis dorsalis to the hypothalamus.

b) Mesencephalon (Fig. 28) (Fig. 29).

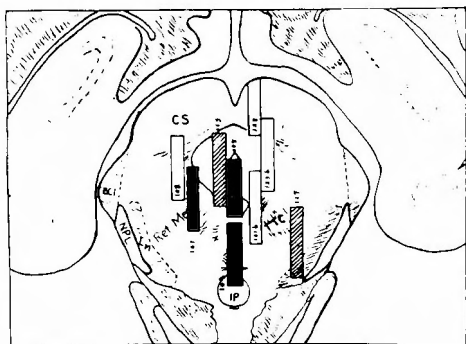


Fig. 28

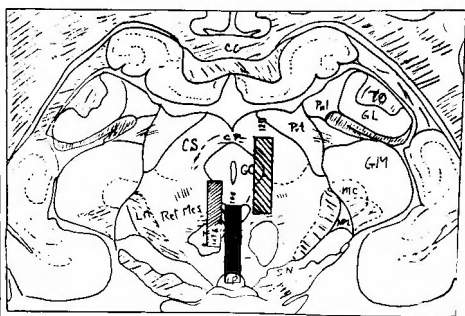


Fig. 29

8 cases out of 12 showed coma or semicoma. Differing results were sometimes obtained from similar shoots. Results were not always constantly related to the portion injured. The shoot aiming at the rostral tip of the midbrain sometimes did not leave any trace of destruction on histological preparation. It seems that the projecting stylet slid into the ventricle without causing a gross damage to the neighboring structures because the tip of the projecting stylet was not sharp. In such a case the cat did not fall into coma but on the contrary showed excitation.

Cat 106 (1st shoot). 2.3 kg, male. (Fig. 30). Coma was produced. Before the shoot, he moved and mewed actively. All noci-reflexes were normal. At the moment of shoot he had stiffness of his trunk and extension of his extremities, which disappeared at the next moment.

* JASPER, H. H. and COSIMO AJMON-MARSAN: A Stereotaxic Atlas of the Diencephalon of the Cat. The National Research Council of Canada, Ottawa, (1951).
Fig. 28~Fig. 32 were also taken from the JASPER's atlas.

For a while after the shoot he was quiet. This animal was not accompanied by a pause in respiration as in experiment I. For 10 seconds following the injury his pinna reflex vanished completely. He ceased his spontaneous movement for 13 seconds. On recovery at first the pinna reflex reappeared, and subsequently he began to move and mew. Thereafter no difference from his condition before the shoot was seen.

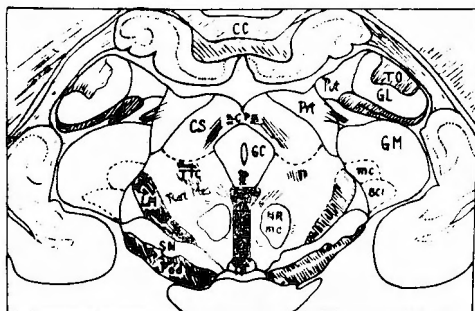


Fig. 30

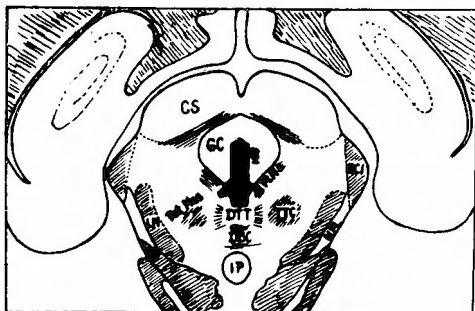


Fig. 31

The electrostimulation was carried out. The shocking machine had been equipped to be used as an electrode and the effect of the electrostimulation on the shot portion was examined utilizing the projecting stylet as a cathode. By stimulation with square pulses of 1.5 volts, 60 per second and 1 msec in pulse duration, the cat lost his noci-reflexes but demonstrated the rigidity of his extremities and trismus. With repetition of the electrostimulation the loss of the noci-reflexes became less clear after a while. The shot portion was located in the midline at the level of the oculomotor nucleus. The destruction involved the interpeduncular nucleus. Measuring from the length of the projecting stylet the shoot was supposed to have started at the ventral end of the central grey matter.

Cat 105 (1st shoot). 1.8 kg, female. (Fig. 31) Coma was produced. At the shoot spastic extension of the extremities took place. Also the cessation of spontaneous movement was noticed for 1'. The noci-reflex was lost for 3" and weak for succeeding 10". A pause of respiration was not seen but the superficial and frequent respiration was present. The cat was somewhat inert after the shoot. Pathological study revealed the hit area to be on the midline of the mesencephalic central grey matter at the level of the oculomotor nucleus.

Cat 123 (2nd shoot). 2.0 kg male. (Fig. 32). No coma was produced. At the shoot there were stiffness of the trunk and spastic extension of the extremities. After the shoot there was the cessation of spontaneous movement for about 25". There was also the cessation of mewing. The pinna reflex was not lost. Pathological study revealed the hit area to be on

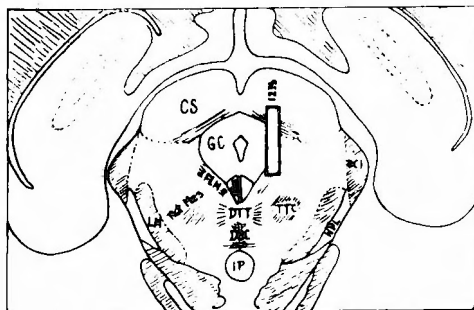


Fig. 32

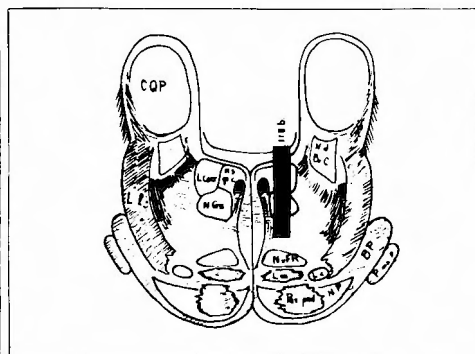


Fig. 33

the right border of the mesencephalic central grey matter and extending partially into the reticular formation.

Cat 107, with the area of destruction in the reticular formation and cat 117 with the destruction in both the reticular formation and lemniscus medialis showed coma and semicoma respectively (cf. Fig. 29).

c) Pons and medulla oblongata

Stiffness of the trunk and extremities was generally more conspicuous than in the case of coma after the shoot of other regions. The cats tended to have a rather accelerated respiration. None of the animals showed the respiratory arrest. In some cases the recovery from coma, i. e. mainly the reappearance of the noci-reflexes was delayed and not as complete as in the midbrain-coma case.

Cat 118 (2nd shoot). 2.0 kg, female. (Fig. 33); Coma was produced. At shoot there was marked stiffness of the whole body and also a pause in respiration. After the shoot the rigidity of the trunk and extremities did not persist. Respiration was steady. There was the loss of the pinna reflex for 10". There was the cessation of spontaneous movement and mewing for 30". Recovery of spontaneous movement was not complete. Pathological study revealed the hit portion to be the locus coeruleus and its neighborhood at the level of caudal end of the colliculus inferior. In this case the shocking machine was inserted at an angle of 15° to the vertical plane anteriorly inclined.

Cat 126 (1st shoot). 2.8 kg, male (Fig. 34) No coma was produced. At the shoot there was stiffness of the trunk and extension of the extremities and the cat screamed loudly once at that moment. After the shoot there was no cessation of spontaneous movement and no loss of pinna reflex. Pathological study revealed the hit portion to be in the reticular formation adjacent to the midline at the level of the intracerebral roots of the Vth and VIth cranial

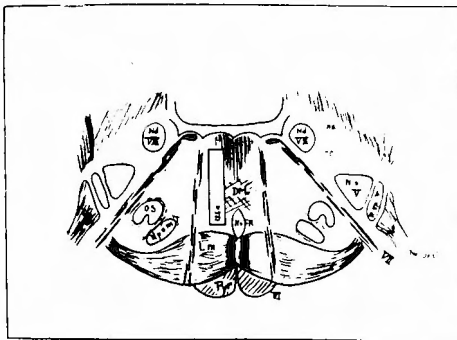


Fig. 34

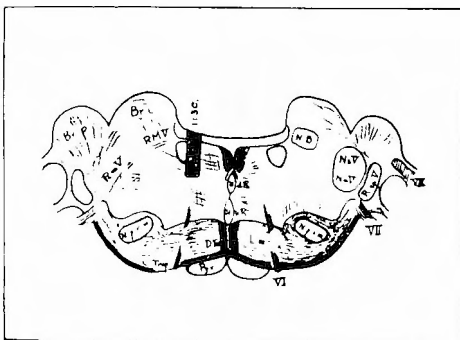


Fig. 35

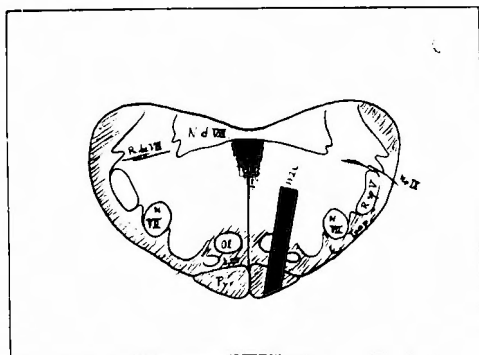
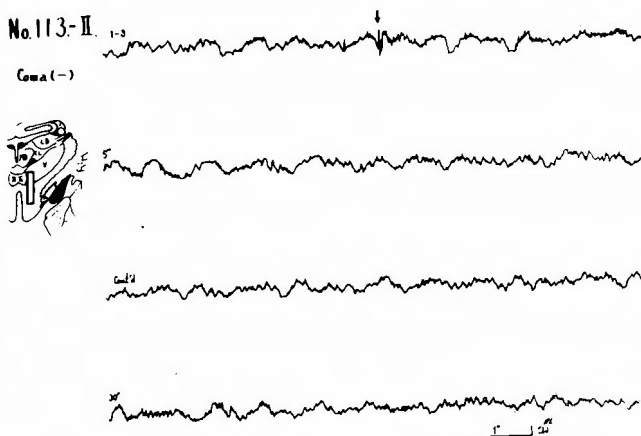
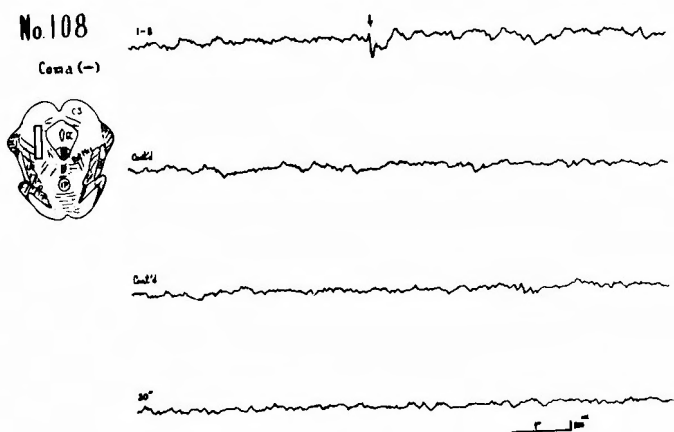
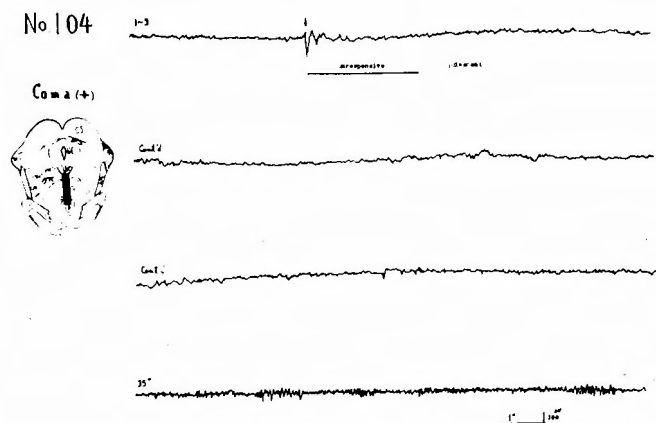


Fig. 36

nerve.

Two additional cases showed coma. In one case there was the destruction in the reticular formation and the floor grey of the fourth ventricle at the level of the intracerebral roots of Vth and VIth cranial nerve. In the other case there was the destruction on the reticular formation, nucleus olivae and pyramidal tract at the level of nucleus dorsalis nervi VIII. (Fig. 35) (Fig. 36).



4) Electroencephalogram (surface EEG)

Cat 104 (Fig. 37). Coma was produced. The animal was completely unconscious for 2 seconds and quiet without movement for succeeding 10 seconds. The hit area was on the

midline extending from the ventral end of the mesencephalic central grey matter to the interpeduncular nucleus. Immediately after the shoot a slight diminution of frequency in EEG was seen. Subsequent waves were not different from pre-shoot ones, but from 40 seconds after the shoot there were spindle bursts of relatively high frequency.

Cat 108 (Fig. 38). No coma was produced. The hit area was in the mesencephalic reticular formation. No difference in frequency and amplitude between the pre-and post-shoot pattern was seen.

Cat 113 (Fig. 39). No coma was produced. The hit portion was in the hypothalamus. Remarkable changes were not found in the post-shoot pattern in this cat.

The EEGs in the present experiment generally did not show any remarkable alteration immediately after the shoot. Although some diminution in frequency was observed in the case of coma, it was not to be considered in relation to coma. The only noticeable change was the occurrence of spindle bursts after the awakening from coma. The paucity of EEG changes may be due to the less violence of trauma and probably also to the lack of severe brain edema in the experiment II.

Discussion

DENNY-BROWN, WALKER and others have experimentally produced the concussion, contusion or laceration by means of a blow inflicted on the surface of the skull or on the exposed dura and observed the physical reactions of these animals. WALKER stated that following reactions or clinical manifestations occurred, although not always: 1) Instantaneous spasm of muscles all over the body at the moment of impact ... he called it "tetanic phenomena" ..., 2) respiratory changes owing to the spasm of the intercostal muscles and diaphragm muscles, 3) rise of blood pressure following the impact with subsequent fall, 4) bradycardia, 5) changes in the reflexes ... temporary disappearance of the tendon reflexes and noci-reflexes and especially a loss of the canthus reflex. We noticed the same manifestations as reported by WALKER with some difference in degree. We hoped that we might have been able to cause similar reactions with use of a mechanical violence restricted to a smaller area of the brain.

We have used the definition of coma as an unresponsive state with associated loss of noci-reflexes. According to ASAI, in our laboratory, even when a cat's brain stem was cut at the rostral level of midbrain, a loss of noci-reflexes was not seen. This procedure corresponds to the *cerveau isolé* of BREMER, but we can not regard this state as coma according to our criteria. In recent years MAGOUN and others have stressed the significance of the rostral part of the mesencephalic reticular formation in the maintenance of consciousness. In comparing our work with theirs much attention should be paid to the difference between their criteria and ours in defining unconsciousness.

In the present investigation 1) coma was caused only temporarily. 2) The most conspicuous coma was induced from the rostral tip of the central grey matter. According to YABUNO nicotization induced temporary coma in this area. 3) It was necessary to inflict the strong and instantaneous impact to cause coma. Slow destruction did not cause coma. Thus we feel that coma might be a result

of excessive stimulation, not of functional loss. A phenomenon such as a local seizure discharge originating from the shot region may have produced coma. If we postulate that the more powerful the penetration is, the more widely the stimulation is exerted on the surrounding tissue, we can understand the facts that in experiment I, obvious coma was induced from the corpora quadrigemina while in experiment II coma was induced not from the corpora quadrigemina but from the central grey matter.

In experiment I, not only the brain stem but also both temporal lobes were penetrated, but it was shown in control experiment that coma was induced also in those cases whose temporal lobes were partially resected prior to the shoot. It was possible that in some cases coma might have been caused by the damage to the hippocampus or the gyrus hippocampi, but the penetration through the colliculus inferior caused coma even though the hippocampus or the gyrus hippocampi was apparently intact; the shoot track was found on the ventroposterior edge of the occipital lobes at a considerable distance from the gyrus hippocampi. On the basis of these facts it would appear that coma was the result of the brain stem injury. From experiment II this assumption seems even more likely.

The coma-area of the brain due to nicotization (MATSUNAGA) was more widely distributed than that in experiment I, and the latter was wider than that in experiment II. That is to say, in experiment I we could not induce coma by the shoot of the gyrus cinguli (gyrus fornicatus), while the nicotization of this area did produce coma. In experiment II we could not produce coma by shooting the hypothalamus, a procedure which induced coma in experiment I. From these facts it is conceivable that if the strength of a blow is increased, the spheres of the brain from which coma might be induced by the blows, would become wider.

At any rate it seems evident that coma (loss of the noci-reflexes) can be more easily induced from the injury to the lower brain stem including the midbrain than from the cerebrum. The regions responsible for coma in our present experiments included the sleep-regulating center by MAUTHNER and VON ECONOMO, i. e. the transitional part from the third ventricle to the aquaeductus SYLVII, the ventro-caudal end of the third ventricle, and the base of the fourth ventricle, the reticular arousal system by MAGOUN, FRENCH, LINDSLEY et al. i. e. the rostral part of the mesencephalic reticular formation, and the sites of predilection of petechial hemorrhage in severe head injuries, i. e. the caudodorsal part of the hypothalamus, the midbrain, the floor of fourth ventricle.

Cerebral Electrical Activities.

In the experimental concussion as done by means of striking the exposed skull of a cat by WILLIAMS and DENNY-BROWN, a diminution of amplitude appeared in the initial period after injury and slow waves were dominant on recovery. They felt that such diminution of amplitude was the direct result of mechanical violence to the cerebral cells, and that slow waves were made by a secondary circulatory disturbance as brain edema. At first in experiment I we had anticipated that coma would be accompanied with a flattening of the EEG, but on the contrary at

the impact on the midbrain (with simultaneous damages to the temporal or occipital lobes) electrical activities were apt to be remaining and immediately after impact there was a tendency toward desynchronized low voltage fast waves. In cases of the hypothalamus shoot, after remaining steady for several seconds following the impact, flattening of EEG appeared and continued. In cases of the telencephalon shoot flattening of the EEG was most conspicuous. From these findings it may be assumed that there is at least no direct relation between the change in cerebral electrical activities (most conspicuous at the telencephalon shoot) and the loss of the noci-reflexes (most frequently seen at the midbrain shoot). We can not suggest at the present stage of our investigations by what mechanism such a change in EEG pattern is caused. It is hard to interpret fast waves or a steady pattern immediately after the impact and a subsequent extremely long period of flattening. The brain edema, however, seemed to play a important role in the flattening of the EEG.

The EEG in experiment II, not related to the affected region nor upon the depth of coma, did not show remarkable changes. We note that in brain stem injuries a loss of the noci-reflex can be caused by the small violence, but apparently severe violence is necessary to cause a change in the EEG, which may probably be the result of diffuse cerebral edema.

Summary

In order to investigate which regions of the brain are most important in the occurrence of traumatic coma, we tested the effects of mechanical trauma locally applied to various portions of the cat's brain. We used two methods. The index of coma in the present investigations consisted of the cessation of spontaneous movement and the loss of the noci-reflexes. Strong impact must be applied to the brain to cause a comatose state. It appeared that coma was caused as a result not of a functional loss owing to the destruction but of an excessive mechanical stimulation. This fact supports previous experiments in our laboratory.

a) In experiment I, a cat's brain from which the temporal bones had been removed bilaterally was penetrated transversely and horizontally with a special impact apparatus constructed modeling after an air-rifle, and the relation between the destroyed portion and coma was investigated. Coma was most conspicuous in penetration of the transitional portion from the aquaeductus SYLVII to the third ventricle, especially on the rostral tip of mesencephalic central grey matter. Penetration of the caudal part of the hypothalamus, of the dorsal portion of the midbrain (central grey matter and corpora quadrigemina) and in the base of the crus cerebri also showed coma or semicoma.

The resulting behavioral changes are not to be regarded as symptoms purely due to brain stem injury because the penetration experiments were accompanied by the simultaneous damage to the bilateral temporal or occipital lobes. However, we feel that coma perhaps may be caused from the brain stem injury because the penetration in the mesencephalon after the partial resection of bilateral temporal lobes also caused coma. It was impossible in our experiment I to shoot the

pons and medulla oblongata for anatomical reasons.

b) In experiment II, a less violent and more restricted shock were applied to the various parts of the brain with a small needle-shaped shocking machine with an elastic spring. Coma was produced by shocking more restricted area than in experiment I, from the midbrain to the rostral part of medulla oblongata. This revealed that the mesencephalic central grey matter and perhaps the nucleus interpeduncularis and the rostral 2/3 part of pontobulbar reticular formation etc. were related to coma.

c) The surface EEGs in experiment II did not show any remarkable changes perhaps because of less violence of injury. In experiment I, the penetration of the telencephalon showed the most conspicuous flattening of EEG, and the penetration of the hypothalamus also showed flattening, while the penetration of the midbrain showed the least remarkable flattening and a tendency of pre-shoot electrical activities to remain. EEG findings and behavioral changes (especially the loss of the noci-reflexes) did not show a parallel relationship.

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(.....*written in Japanese.)

和 文 抄 録

頭部外傷による昏睡の実験的研究

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脳外傷の場合、脳のどの部位の損傷が、最も昏睡に深い関係があるかを検索するため、次の2方法で、機械的（力学的）侵襲を脳の各部に局所的に加え、自発運動の停止と、侵害反射の消失を、昏睡判定の主たる指標として検査した。昏睡を起すためには、急激且つ強度の衝撃を加えることが必要であつて、本教室に於ける他の実験で知られていたと同様に、徐々なる破壊による単なる機能脱落の結果としては起らなかった。

a) 実験Ⅰは、開頭猫の脳を、空気銃型衝撃器を以て、前額断面内水平方向に射抜き、損傷部位と、昏睡との関係を検討した。それによると、中脳水道吻端、そこから第3脳室に移行する部分を通つたものに、昏睡が最も顕著で、視床下部後端や、中脳背側（中脳中心灰白質より四丘体にかけた部分）又は大脳脚底を通つたものに昏睡、半昏睡を認めた。尚、橋脳、延髄の貫通射撃実験は、この部の解剖学的関係から、実行出来なかつた。

これら貫通射撃は、同時に側頭葉をも貫くので、純粋に脳幹からのみの症状とは断じ得ないが側頭葉に小切除を施し、そこを通つて貫通させても昏睡が起つた

から、脳幹性の昏睡と考へてよいと思う。

b) 実験Ⅱは、射撃の影響を更に細かく局部的に検するため、穿刺針の尖端から、マンドリンが弾発的に飛出す装置を作り、脳幹各部を小さく衝撃した。これによつて、昏睡を来す範囲は、実験Ⅰより更に狭く、中脳以下延髄の吻側部迄で、中脳中心灰白質、恐らく中脳網様織並に、脚間核、及び菱形窩前2/3の網様織が昏睡成立に関与するもののようである。尚実験では、必ずしも同一部位の衝撃で、常に同一結果を得るとは限らなかつた。

実験Ⅰ、Ⅱを合せ考えると、中脳から延髄吻側部迄が最も昏睡を起し易く、視床下部がそれに次ぐと思われる。

c) 脳波は、実験Ⅱでは、恐らく衝撃が小さすぎた為か、著変を示さず、実験Ⅰでは、終脳内のみを貫通したものが、最も顕著な平坦化を示し、視床下を通過したものも、平坦化するが、中脳を通過したものは最も平坦化し難く、且つ射撃前の脳波が最も残存し易い。即ち、脳波所見と、態度上の変化、殊に侵害反射の消失とは、平行関係を示さなかつた。