LOCALIZATION OF AN EXPERIMENTAL HYPO-
THALAMIC AND MIDBRAIN SYNDROME
SIMULATING SLEEP [1]

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FIFTEEN FIGURES

The origin and significance of sleep have been a source of
speculation throughout the centuries, and the problem of
abnormal sleep as a disease entity has long aroused the
curiosity of medical men. It was only half a century ago,
however, that Mauthner (1890), after studying clinical cases
of Nona and Wernicke's disease, postulated a specific locality
in the brain as a critical source for sleep regulation. This
center he designated the area of transition between the mid-
brain and the diencephalon.

More recently, von Economo ('29, '30, '31), from his study
of encephalitis lethargica during the Vienna epidemic of
1916–17 and 1920–21, came to conclusions similar to those
of Mauthner and proposed certain rostro-caudal boundaries
to delimit the center: the most caudal limit being immediately
rostral to the oculomotor nucleus and the frontal limit reach-
ing as far as the region of the striatum.

The historical distinction between normal and abnormal sleep was made by Kleitman also in 1929. He defined the criteria for normal sleep as: (1) loss of critical reactivity to environmental events; (2) increased threshold of general sensibility and reflex irritability; (3) ability to be aroused or brought back to the state of wakefulness. This statement has served as a practical norm in subsequent experimentation (Kleitman, '32; and Kleitman and Doktorsky, '33), including the present study. Although experiments on normal sleep are based largely upon physiological data and the overt characteristics of sleep in normal persons, experiments involving induction of aberrant sleep, such as those considered in the present study, must be confined to animals.

With the development of the Horsley-Clarke stereotaxic instrument about 1905 by Clarke (see Horsley and Clarke, '08) in England, the stage was set for experimentation in the mammalian brain to depths which had previously been inaccessible. Attempts were made to duplicate, electrically, nature-made lesions which had resulted in abnormal sleep; moreover, by the use of this instrument, stimulation as well as destruction of an area was possible.

Ranson ('39) published an account of diencephalic lesions produced in 55 monkeys with the Horsley-Clarke instrument. Of these monkeys, only the 10 animals having large lesions in the lateral hypothalamic area consistently showed somnolence. From these positive results, he concluded that bilateral destruction of the lateral hypothalamic areas led to somnolence; and that the same areas, when stimulated, produced combined sympathetic and somatic excitation, i.e., just the reverse of the behavior seen during sleep. He further postulated that the somnolence was due primarily to the elimination of the downward drive through descending pathways with origin in those nuclei of the hypothalamus functionally related to sympathetic responses. Such pathways continue caudally through the lateral hypothalamic area into the midbrain.

On the basis of positive results obtained from 22 cats out of 54 cats experimented upon, Harrison ('40) corroborated Ranson's findings, namely that somnolence occurs with bilateral destruction of the lateral hypothalamic area just rostral to the mammillary bodies. Catalepsy tended to develop in these cases when the lesions involved the medial and caudal parts of the hypothalamus. Ranson and Ingram ('32) obtained 8 cataleptic cats having similar lesions extending into the tegmentum of the midbrain immediately behind the ventral part of the hypothalamus.

Nauta ('46), working on rats, duplicated Ranson's results and agreed that the lateral hypothalamic area seemed to be of more importance for regulating sleep and waking than the more medial hypothalamic areas; he noted further that somnolence occurs most consistently in the rats with bilateral lesions at mammillary body level, but that bilateral lesions at infundibular level and unilateral lesions at mammillary body level produce drowsiness. Nauta therefore concluded that the degree of somnolence is proportional to the number of ascending fibers in the medial forebrain bundle which have been interrupted, and that the waking center itself lies in the region caudal to the mammillary body, i.e., in the midbrain tegmentum. This latter conclusion clearly differs with that of Ranson ('39) as stated above.

Krieg ('32) had observed, in the rat, fibers arising in the hypothalamic nuclei and joining the medial forebrain bundle in the lateral hypothalamic area. Ranson and Magoun ('39) suggested that the fibers in the rostral part of the medial forebrain bundle end in the hypothalamic nuclei and are replaced by other descending fibers which originate in the hypothalamus and turn backward through the lateral hypothalamic area into the midbrain.

Then on the basis of previous experiments involving stimulation, Ranson et al. (Magoun, '40) concluded that the descending hypothalamic fibers scatter dorsally at the level of the mammillary bodies; the greater number continue directly into the midbrain tegmentum, but the remainder turn medially

into the central gray surrounding the aqueduct. However, Ranson reported that the relative importance of the two fiber systems could not be evaluated by this stimulative method.

Crosby and Woodburne ('51) described hypothalamo-tegmental systems of fibers in normal monkeys. From the anterior and posterior parts of the medial hypothalamic nuclei, fibers enter the lateral hypothalamic area to lie ventromedial to the medial forebrain bundle with the more posteriorly-arising fibers situated most ventromedially. Such fibers continue into the midbrain where most of them end, after partial decussation in the supramammillary commissure, in the ventral portion of the deep mesencephalic nucleus. Other more dorsally situated fibers turn back into the midbrain directly from the posterior hypothalamus to end in the dorsal part of the deep mesencephalic nucleus.

Whittier and Mettler ('49b) produced somnolence in 4 monkeys in a series of experiments on 80 monkeys with bilateral lesions in the subthalamic nucleus. Probably they had damaged the lateral hypothalamic area which is directly medial to the subthalamic nucleus and the lenticular fasciculus both of which were injured in these 4 cases. They obtained somatic characteristics of somnolence but apparently found no visceral effects such as those which would be indicated by changes in temperature or in rate of respiration.

The experimenters mentioned above, namely Ranson et al., Harrison, and Nauta, working on monkeys, cats, and rats respectively, produced somnolence by destroying relatively large areas in the hypothalamus. The obvious limitations of this procedure were first intimated by Ranson and Ingram ('32) and later expressed by Whittier and Mettler ('49a). Such methods do not reveal precisely the function of small regions with respect to the various somatic and visceral elements characterizing sleep and drowsiness, nor do they permit the tracing of degeneration in specific fiber tracts. Therefore, in the experiments on the Macaca mulatta hereinafter described, it was proposed to explore by use of stereotaxic apparatus various levels within the limited region of

the lateral hypothalamic area and the adjoining rostral midbrain tegmentum and to trace the descending fibers of the medial forebrain bundle which degenerated following lesions that make it impossible for the animal to stay awake.

MATERIAL AND METHODS

This experimental study was carried out on 7 small Macaca mulatta monkeys about two years of age, weighing between 5 and 7 pounds. Daily controls of rectal temperature, respiratory rate and heart rate were recorded. Appetite, posture, motor activity and emotional responses were observed for several days prior to operation. When possible, early morning and late afternoon rectal temperatures were recorded to discover the daily fluctuations. For this procedure, the animal was held by one person while a second checked the temperature, observed the respiratory excursions and felt the heart rate over the thorax.

A single operation or a series of operations, either bilateral or unilateral, were performed on each monkey, using the McCulloch stereotaxic apparatus to locate the desired sites (Atlas and Ingram, '37) for the electrolytic lesions. These sites were either in the caudal hypothalamus or in the rostral midbrain tegmentum. Operations were repeated at approximately weekly intervals until positive results were obtained or until the exitus of the subject. Ether was the only anesthetic agent used. For the monkeys in which the body temperature dropped several degrees following operation, heat lamps were introduced to supplement the body mechanisms for maintaining body temperature. In cases where the appetite was negligible, spoon feeding was initiated to carry the animal through its difficult days.

Post-operative changes in rectal temperature, heart rate, respiratory rate and in behavior were noted for the macaques. The purpose of these data was to establish the extent and characteristics of the somnolence or drowsiness following the lesions.

If the monkey remained alive for an interval of 18 to 24 days after the successful operation, the animal was then anesthetized and perfused with 15% formalin or, in the case of monkey no. 1, with 5% anhydrous magnesium sulfate and 2% potassium bichromate; the brain was removed and prepared for microscopic study by the Swank-Davenport ('35) modification of the Marchi technique for staining degenerated myelin. The Marchi-prepared sections, 25 μ in thickness, were compared with two Weil-stained series and one toluidine blue series of normal macaque brains available from the Huber Neurological Collection of the University of Michigan.

EXPERIMENTAL AND ANATOMICAL RESULTS

Of the 7 monkeys studied, 4 showed signs indicative of some degree of somnolence for periods ranging from 6 days to 24 hours; two others were completely negative until death; still another exhibited tremor and torticollis only. Of the 4 available somnolent monkeys, one died a respiratory death during a bilateral operation. The remaining three somnolent monkeys, along with the one monkey showing tremor and torticollis, were sacrificed for microscopic study. Thus a total of 4 brains were studied using Marchi technique.

Monkey no. 1

Protocol. February 18, 1949. Bilateral lesions were placed — presumably in the hypothalamus — by use of the stereotaxic apparatus. Four hours after the operation, the only abnormal effects were unequal pupils, the right being larger than the left, and an occasional shiver-like body tremor, especially noticeable in the limbs. Within 96 hours post-operatively, there was also a slight ptosis of the right eye-lid.

February 22, 1949, a second operation was performed by a similar technique. Twenty-four hours later, the hind limbs showed weakness, for the animal climbed rather than jumped from the window ledge in the cage. There was a changed emotional response; the animal, which had not been quarrel-

some before the operation, snapped at other monkeys who approached her. Two days after the second operation, however, when the room was quiet and she was undisturbed, the monkey sat with her head between her front paws on several occasions as if sleepy and was not so hard to catch as previously. Respiratory and heart rates were subnormal; the morning rectal temperature was 1°C. above normal.[3] Six days after the second operation, the right pupil remained larger than the left. The animals was still tame.

March 1, 1949, the third bilateral operation was performed. During the operation, while lesions were being made on the right, movements of the hind limbs were elicited along with grunting noises and facial grimaces. During the placing of the most caudal right lesion, respiration was slow and deep, a shallow breath being interpolated between each deep inspiration and expiration. Upon infliction of the lesions on the left, a horizontal nystagmus of the right eye was noticed, with the slow component to the left; at the same time, the left eye was turned laterally. Although no ether was given during the closing of the skin incision, the monkey was unusually quiet and kept both eyes closed.

Several hours post-operatively, the rectal temperature [4] had risen to 40.7°C. at 4 P.M.; respiratory rate was slightly decreased but heart rate was normal. The light reflexes were abolished and both pupils were dilated, the right more than the left; there was ptosis of both lids, more marked on the right, but the monkey could open the lids when there was sufficiently strong external stimulus. Although no paralysis of the limbs was evident, the animal exhibited a cataleptic posture for hours at a time. Most commonly the animal lay crouched on all fours or sat up on her hind legs, resting the forelegs on the wall of the cage. Except for the erratic movements of the hind limbs, there was a distinct lack of emotional response when the thermometer was placed in the rectum,

[3] Pre-operative diurnal range of rectal temperature in monkey no. 1: A.M. 38.3°C. and P.M. 40.1°C.

[4] See footnote 3.

although previously she had reacted violently to this daily procedure by kicking and grunting.

Twenty-four hours after the third operation, the rectal temperature had taken a sudden drop to 36.1°C. (2° below normal) at 9 A.M., increasing to 37.3°C. (2.5° below normal) by 4 P.M. This diurnal rise was coincidental with a similar increment in room temperature. Respiratory rate was reduced but heart rate was normal. Both eye-lids were ptosed as before, but the animal shut them tightly against attempts to force them open. Activity was minimal and the tendency for prolonged catalepsy remained. Occasionally there were short periods of gross clonic body tremor which might occur spontaneously, but which were more frequent when the animal was picked up or fed. The pronounced apathy extended to food. Food when placed in the mouth was chewed and swallowed, but with diminished speed and strength of bite; some food often remained in the mouth in spite of the temporarily successful attempts to stimulate chewing by pulling down the mandible or tugging at the food held between the teeth.

Lamps were used during the night to maintain the cage temperature so that 48 hours after the third operation, the rectal temperature at 9 A.M. was 37.9°C. (0.5° below normal), an increase of almost 2° over the temperature of the previous day at the same hour. By 5 P.M. it had decreased to 37.4°C. (2.5° below normal), thus reaching the low of the previous day in spite of the lamps. The monkey remained expressionless, sat motionless with the head bowed and eyes closed for hours. She altered this position only to stand with the front legs leaning against the wall of the cage, but with the head bowed. Only loud noises could cause the animal to raise the head momentarily and open the eyes. The only resistance offered to holding and spoon feeding was a few weak grunts, spontaneous rapid body jerks and erratic kicking movements. Both eye-lids showed edema. While posed by the observer in various unusual positions, the monkey was photographed (figs. 5 and 6). Complete unconcern was displayed toward

the necessary manipulations, the assumed poses and the new surroundings. The eyes remained closed.

Three days after the third operation, the monkey was still the same apathetic, motionless, bowed, anorexic animal as before. The heart rate was now reduced. Some loss in weight had occurred perhaps because of dehydration. After feeding on this day, the monkey was observed resting her chin in the water trough, but she evidently did not swallow much water. The left eye was open for most of the feeding time, but the right eye remained almost closed.

Seven days after the third operation, the respiratory and heart rates were still reduced; the rectal temperature was 35.1°C. (3.5° below normal) at 9 A.M. and 36.6°C. (3.5° below normal) at 4 P.M., with the room temperature the same at both times. The monkey still retained the same odd postures for hours, but responded more readily to loud noises by jerking her body or turning the head toward the noise; however, she became refractory after the first response. Upon repeated visits to the room, her eyes opened and the head was lifted, but her expression remained dazed; within a few minutes, there was a return to the apathetic condition. For the first time since the third operation, the animal showed signs of regaining her appetite by occasionally picking up an apple slice, taking one or two bites, and then holding it poised in mid-air before dropping it. The same body jerks occurred when the animal was held for feeding.

Eight days after the third operation, the animal not only kicked, but cried lustily for the first time since the operation when held for feeding. The monkey now showed signs of recognition of an intruder.

Fourteen days after the third operation, the rectal temperature[5] reached its lowest < 34.4°C. (more than 4° below normal) at 9 A.M. along with a correspondingly low room temperature; the respiratory and heart rates were at their lowest. The posture was more erect than previously and body

[5] The animal's temperature was below the minimal reading of 34.4°C for the thermometer.

position was shifted more frequently. Only rarely were the eyes found to be closed. Discrimination among foods was now shown, bread with peanut butter being preferred to plain bread. Raisins, the favorite food, were picked up in the two paws alternately. However, the animal was still so docile when handled that protective gloves were unnecessary.

Seventeen days after the third operation, for the first time since that procedure, she showed response to fear by jumping back from a stimulus such as a jet of air blown across her face or a suddenly outstretched hand obstructing her vision. The rectal temperature at 4 P.M. was 35.1°C. (5° subnormal).

Twenty-three days after the third operation, the rectal temperature was 37.6°C. (1° below normal) at 9 A.M., and was 38.8°C. (1° below normal) at 4 P.M.; the heart rate was almost normal and the respiratory rate was approaching normal. Only the right lid remained slightly ptosed; both pupils were dilated, the right being the larger. There was still no response to increased light.

On March 25, 1949, 24 days after the third operation, the animal was sacrificed and the brain prepared for microscopic study by the Marchi technique.

Location of lesions and degeneration (figs. 1–4). The needle pierced the cerebral cortex bilaterally in area 6 just anterior to motor area 4, about 2–3 mm from the mid-sagittal plane. It continued parallel to that plane, through the head of the caudate nucleus and the anterior commissure, to reach the lateral hypothalamic area at infundibular levels. During the third operation, the needle on the left also passed through the rostral end of the dorsal thalamus between the anterior and the lateral nuclear groups to reach the mammillary body; more caudally it traversed the lateral and dorsomedial nuclei of the dorsal thalamus to enter the red nucleus of the midbrain at the level of the oculomotor nerve roots.

Hypothalamus. The lateral hypothalamic area is destroyed bilaterally from the caudal end of the optic chiasma to the caudal end of the tuber region. Only on the left is the destruction carried farther caudally through the level of the mam-

millary body. Just ventral to the ansa lenticularis, in the lateral hypothalamic area of the right side, is a degenerated longitudinal group of fibers. This cylindrical bundle is flattened out obliquely, dorsomedially and ventrolaterally. It can be traced caudally from the lesion at the tuber level, where it is in a position dorsolateral to the mammillary body and dorsomedial to the cerebral peduncle, to the level of the oculomotor nerve roots. It represents the ventral part of the posterior hypothalamo-tegmental fibers but includes some of the anterior hypothalamo-tegmental fibers of Crosby and Woodburne ('51). The bundle tapers off laterally to a few fibers which pass longitudinally along the dorsal border of the subthalamic nucleus; another small group of fibers passes through the medial tip of the subthalamic portion of the substantia nigra. On the left side, the lesion itself is large enough to include the above mentioned hypothalamo-tegmental fibers; therefore no degeneration can be traced.

The caudal end of the optic chiasma is partially involved on the left and the rostrodorsal part of the optic tract is injured on the right. Consequently there is a degeneration of the caudomedial tip of each optic tract as it passes dorsolaterally towards its respective lateral geniculate nucleus, which also shows slight degeneration in its dorsomedial portion. The dorsal supraoptic commissure at the caudal level of the optic chiasma is included in the lesion bilaterally with resulting degeneration across the midline as well as lateral to the lesion, which extends into the inner half of the globus pallidus. The supraoptic nucleus is involved bilaterally at this level. At the rostral level of the optic tracts, the supraoptico-hypophyseal tract is degenerated bilaterally from the paired lesions laterally to the supraoptic nuclei. The diffuse supraoptic nucleus is damaged bilaterally at this level.

The medial hypothalamic area is severely damaged on the left side from the rostral infundibular level to the midbrain, but there is only slight damage on the right. Included on the left side, throughout infundibular and tuber regions, are the perifornical nucleus, almost the entire dorsomedial hypo-

thalamic nucleus, and the lateral half of the ventromedial hypothalamic nucleus; at infundibular level there is degeneration of the medial half of the ventromedial hypothalamic nucleus; throughout the tuber region, the posterior hypothalamic nucleus and the dorsomedial hypothalamic nucleus are involved. Damaged on the right side only at infundibular and tuber levels are the paraventricular nucleus and the dorsal hypothalamic area. The dorsomedial hypothalamic nucleus is involved at tuber level. At infundibular level, there is bilateral degeneration of a few fibers which pass obliquely medioventrally from the globus pallidus through the fornix to end respectively in the ipsilateral perifornical and ventromedial hypothalamic nuclei, the so-called pallido-hypothalamic fibers, of Ranson and Ranson ('39).

The more discrete structures involved on the left side at mammillary body level are: the mammillary body, including both its medial and lateral nuclei, the fornix, the mammillothalamic tract (just dorsal to the mammillary body), and the mammillo-tegmental tract forming just lateral to that body. Immediately caudal to the mammillary body on the left, supramammillary decussation is involved with a resulting slight degeneration across the midline that cannot be traced laterally.

Subthalamus. The medial half of the zona incerta is involved bilaterally at the caudal level of the optic chiasma; on the right, the lesion extends caudally to infundibular level and includes also the lateral part of the zona incerta. The subthalamic nucleus is damaged on the right at its most rostrolateral tip.

The medial half of the substantia nigra at the mid-level of the mammillary body on the right falls within the lesion. Degeneration of the fibers within it extends through the midbrain. The red nucleus on the left is included from its rostral limits in the subthalamus. The ansa lenticularis is probably involved on the right as it swings around the internal capsule, as is also a part of the lenticular fasciculus on the same side as it passes dorsal to the subthalamic nucleus.

On the left, the lesion includes both the ansa lenticularis and the lenticular fasciculus.

Midbrain. The red nucleus on the left is involved from its small-celled part in the subthalamus to its caudal midbrain level. Striking degeneration was observed in the large fibers which arise here and cross the midline obliquely from dorsal to ventral in the ventral tegmental decussation to form a compact band of fibers ventral to the decussation of the brachium conjunctivum. These fibers continue caudally as a part of the rubro-bulbar and -spinal tracts. A few of these heavily degenerated fibers leave the tract to continue dorsolaterally where they join the brachium conjunctivum and the incerto-tegmento-olivary tract (Woodburne, Crosby and McCotter, '46) as possibly the rubro-olivary tract (Papez, '42), although sections of the brain are not available below the mid-pons level. At the caudal end of the lesion on the left, the most lateral oculomotor nerve roots are damaged.

The substantia nigra on the right, as a result of its sub-thalamic lesion, shows gross degeneration of fibers continuing to the hindmost limit of the midbrain, where the degeneration diminishes gradually while moving dorsolaterally to disappear in the proximity of the lateral part of the deep mesencephalic nucleus. The affected fibers may be labeled the nigro-tegmental tract. A few fibers may continue on into the superior colliculus as the nigro-tectal tract.

Just dorsal to the medial third of the substantia nigra on the right is the distinctly degenerated bundle of hypothalamo-tegmental fibers (Crosby and Woodburne, '51), which can be traced from the lateral hypothalamus to the level of the oculo-motor nerve roots where the fibers spread out between the oculomotor roots to disappear in the ventral part of the deep mesencephalic nucleus.

On the right, there is degeneration of the medial tip of the cerebral peduncle from a lesion at its rostral end. The degeneration continues caudally into the base of the pons, beyond which no sections were traced.

Basal ganglia. There are scattered degeneration granules bilaterally in the inner half of globus pallidus, especially on the right.

Monkey no. 2

Protocol. September 24, 1949, 6 hours after a bilateral operation, the monkey lay quietly with his eyes closed while being checked for rectal temperature. When in his cage, he continued lying on all 4 legs and kept his eyes closed as long as the room was quiet. The right lid was half ptosed and the right pupil was dilated. His appetite was poor and the animal chose to eat only a few apple slices by himself, throwing the bread offered him to the floor of the cage. The afternoon rectal temperature was subnormal 1°C.; the respiratory rate was decreased 12 excursions per minute, but heart rate remained normal.

On the third post-operative day his rectal temperature and respiratory rate were almost normal. When in the cage with the other monkeys, he was moderately active and observant. However, when separated from the other monkeys and held from behind by his forelimbs, he almost immediately bowed his head, closed his eyes and remained motionless. Even when placed on one's lap, he made no attempt to escape and lay quietly until aroused by some potent stimulus like air blown across his face or loud clapping or shouting. Of the various stimuli, the air current remained the most effective, for he built up a tolerance to the others after a few trials.

Four days post-operatively, the animal was still sufficiently drowsy to be quietly posed with his eyes closed for a picture (fig. 11).

Seven days post-operatively, there was only a slight tendency for the monkey to close his eyes and he opened them at the least noise, even when kept in a room by himself. His appetite was almost normal, and motor initiative was improved.

Ten days post-operatively, the ptosis of the right eye-lid had disappeared, leaving the right pupil still dilated. There was only a moderate tendency for the monkey to close his

eyes when separated from the other monkeys. He was easily disturbed by any noise and therefore shut his eyes for only a few seconds. It would have been difficult to photograph him at this stage.

October 17, 1949, 23 days after the operation, the monkey was sacrificed, and the brain was prepared for microscopical study.

Location of lesions and degeneration (figs. 7–10). An attempt was made to duplicate the effective lesions in monkey no. 1, using a similar approach to the hypothalamus. The needle passed through the lateral hypothalamic area only on the right at tuber and at mammillary body levels, whereas it passed through the subthalamic area bilaterally. Farther caudally, the tip of the lesion on the right reached the oculomotor nerve roots.

Hypothalamus. In the caudal supraoptic region, there are two groups of heavily degenerated fibers. One of these is the supraoptico-hypophyseal tract. A more dorsal group of degenerated fascicles swings ventromedially across the midline from the medial tip of the internal capsule to the region of the lesion.

On the right, degenerated fibers can be traced to the medial nucleus of the mammillary body where they are injured as they turn through the internal capsule from the globus pallidus. These are not the fibers commonly referred to as the so-called pallido-hypothalamic fibers which were damaged in monkey no. 1.

The supramammillary decussation at the caudal level of the mammillary body contains degenerated fibers which approach the globus pallidus on the left. These fibers were injured in passing through the internal capsule from the region of the right globus pallidus.

The middle third of the right lateral hypothalamic area is destroyed at tuber levels and its lateral third at mammillary body levels. Caudal to the mammillary level, in the region ventral to the ansa lenticularis, a degenerated longitudinal bundle of fibers can be followed to the plane of the oculomotor

nerve roots where it disappears. As mentioned for monkey no. 1, this tract corresponds to the ventral part of the posterior hypothalamo-tegmental fibers described by Crosby and Woodburne ('51).

Subthalamus. The rostral portion of the subthalamic nucleus and the lateral half of the zona incerta are involved bilaterally at tuber and at mammillary body levels. The substantia nigra is destroyed bilaterally at mammillary body levels.

On the right, the ansa lenticularis is included in the lesion at tuber level. Bilaterally, the lesion includes the lenticular fasciculus as it curves through the internal capsule from the globus pallidus at rostral mammillary body levels. The thalamic fasciculus is degenerated bilaterally as it swings dorsally into the ventral nuclei of the dorsal thalamus.

Midbrain. The substantia nigra is degenerated bilaterally throughout, with the lesions in its subthalamic portions. In the dorsal part of the degenerated ventral hypothalamo-tegmental fibers, there are a few fine fibers which cross in the midbrain portion of the commissure of Forel or the supramammillary decussation, to disappear in the ventral part of the deep mesencephalic nucleus of the side opposite the termination of most of the fibers.

The more rostral fibers of the oculomotor rootlets are injured on the right. (A fact related to the ptosis and loss of light reflex on this side.) This injury was partly near their emergence and partly after their emergence from the brain.

The medial tip of the rostral end of the cerebral peduncle is injured bilaterally and is degenerated caudally into the base of the pons, as far as sections were traced.

Basal ganglia. The medial portion of the globus pallidus at the level of the tuber shows slight scattered degeneration bilaterally.

Monkey no. 3

Protocol. A series of three unilateral operations were performed. July 20, 1949, during the first operation, respiration

stopped suddenly after a single lesion was made on the right side. Following a brief period of artificial respiration, natural breathing returned slowly — one deep mouth inspiration every 5 to 10 seconds, the alae nasae dilating several times between each deep inspiration. At the same moment that breathing ceased, the animal emitted a cry. Since monkey no. 7 had just died a respiratory death following a bilateral operation in the same region of the brain, no further lesions were attempted at this time.

Immediately post-operatively, the hind limbs were extended and hypertonic, with no grasp reflex present. The forelimbs were flexed and the grasp reflex was present. Respiration was normal and there were no oculomotor nerve involvements.

Four hours after the first operation, the animal was sitting up in his cage with his head bent forward. Attention was minimal and there was absence of any emotional response. The monkey eyed the observer vacantly, making no attempt to escape through the open cage door. Shortly he closed his eyes, nodded his head and leaned to the left like an inebriated person. The animal had no appetite and made no attempt to bite when held.

Twenty-four hours post-operatively (at 9 A.M.) the rectal temperature was 37.9°C. (0.5° subnormal) and by 5 P.M. it had increased to 38.6°C. (1° subnormal); both respiratory and heart rates were subnormal. The monkey sat erect, growled and pawed when apporached, and once attempted to bite. There was little evidence of an appetite for food, except for smacking movements of the lips and nibbling on bread placed in his paw. Placing and righting reflexes were present; the placing movements with the left front paw were slower than were those with the right.

Forty-eight hours after the first operation, the rectal temperature was the same as on the previous day. While being pulled from the side of the cage, the monkey showed body jerks similar to those so evident in monkey no. 1.

July 23, 1949, the second operation was performed; a single lesion was made on the left to correspond with that on

the right. During stimulation respiration was slowed but did not stop. However, inducing anesthesia was difficult during the remanider of the operation because the animal would hold his breath in inspiration. After the operation, respiration and heart rate were nearly normal. Rectal temperature was reduced as previous to the second operation.

Forty-eight hours after the second operation, the monkey appeared lively, but was refractory to external stimuli such as banging on the cage, for he did not respond by jumping or facial grimaces as do normal monkeys. When the room was still, the monkey lay down and closed his eyes, but re-opened them upon hearing the slightest sound. An attempt to snap his picture failed because the heat and brilliance of the flood lights made him restless.

Three days after the second operation, the rectal temperature was still lowered. The monkey took active defense measures for the first time by jumping quickly beyond reach and by pawing and biting when cornered.

July 27, 1949, 4 days after the second operation, the third unilateral operation was performed, again on the left side. While the lesion was being made, respiration became very irregular, fast and shallow. A few seconds after the lesion had been made, respiration almost stopped and the animal cried out. Artificial respiration was applied immediately and breathing resumed within a few minutes, at a lower and deeper pace. Immediately following the operation, both the head and the eyes were turned to the right. All 4 limbs were slightly spastic. The animal was more docile than just previous to the third operation and emotional expression was limited. The appetite was fair and there was no noticeable tendency to maintain awkward body postures or to sit with the eyes closed.

On the days following the third operation, the afternoon rectal temperature remained subnormal. On the 7th day, the rectal temperature at 9 A.M. was 38.2°C. and at 5 P.M. 38.6°C. (1° subnormal); the respiratory and heart rates were slightly subnormal.

Twelve days after the third operation, the animal was sacrificed and the brain was prepared for microscopic study as before.

Location of lesions and degeneration. The needle pierced area 6 of the frontal cortex bilaterally about 12 mm from the mid-sagittal plane at an angle of 15° from the vertical, and then passed through the globus pallidus, the substantia nigra and the pes pedunculi on the right and through the internal capsule, the subthalamic nucleus and the substantia nigra on the left.

Hypothalamus. The lateral hypothalamic area is intact bilaterally. As in monkey no. 2, there are bilaterally degenerated fibers from the lenticular fasciculus which join the mammillo-thalamic tract to terminate in the medial and lateral mammillary nuclei. The lesion causing this degeneration is in the globus pallidus on the right and in the field H_2 of Forel on the left. A few degenerated fibers in the mammillary peduncle can be traced from the hypothalamus, where they lie lateral to the mammillary bodies, into the midbrain where they disappear at the level of the oculomotor nerve roots, anterior to the ventral part of the posterior hypothalamo-tegmental fibers.

Subthalamus. On the left, the zona incerta and the subthalamic nucleus are included in the lesion at rostral mammillary body level. The substantia nigra is included bilaterally from mammillary body level caudally into the midbrain.

The lenticular fasciculus shows degeneration bilaterally following a lesion in the inner part of the globus pallidus on the right and in the fasciculus fibers arching dorsal to the subthalamic nucleus on the left. A few pallido-hypothalamic fibers on the left can be traced to the ventromedial hypothalamic nucleus and other fibers to the mammillary body of the hypothalamus. A number of bilaterally damaged fibers from the thalamic fasciculus can be traced as they enter the ventral nucleus of the dorsal thalamus. As in monkeys no. 1 and no. 2, there is a slight bilateral degeneration of descending fibers from the ventral part of the lenticular fasciculus

as they arch dorsal to the subthalamic nucleus and continue caudally, dorsolateral to and contiguous with the hypothalamo-tegmental fibers. These fibers possibly represent some of the pallido-interpeduncular fibers of Mettler ('45) and the pallido-subrubral tract of Whittier and Mettler ('49a).

Midbrain. The substantia nigra is damaged bilaterally to the level of the emerging oculomotor nerve roots, involving the medial two-thirds of the nucleus; fibers within it are degenerated to its caudal end.

There is a lesion of the medial tip of the cerebral peduncle on the left and of its middle third on the right, with degeneration continuing into the pons, where it is scattered through the basilar part on the right and limited to the medial tip on the left.

On the right, the lateral-most fibers of the ventral hypo-thalamo-tegmental fibers are damaged at the rostral end of the midbrain tegmentum, just dorsal to the lesion of the substantia nigra. This partially degenerated longitudinal bundle of fibers on the right and a few scattered lenticular fasciculus fibers on the left continue to the level of the oculomotor nerve roots and disappear between the roots. The tract is not so completely degenerated as in monkeys no. 1 and no. 2.

Basal ganglia. The dorsal part of the putamen and the globus pallidus on the right are included in the lesion.

Monkey no. 4

Protocol. Six months previous to this study, the monkey had suffered a bilateral parietal lobe operation.

October 10, 1949, a single left lesion was produced. While the lesion was being inflicted, respiration stopped in inspiration and the electric current was cut off until respiration again became regular. Immediately after the operation, the animal had a marked, fine, postural tremor of the limbs, more evident on the right side. It could be exaggerated by flexing the limbs.

Twenty-four hours after the operation, the rectal temperature at 4 P.M. was 38.0°C. (2° subnormal); respiratory and

heart rates were slightly subnormal. There was a pronounced torticollis to the right and athetoid movements of the head toward that side. When disturbed, the animal would circle to the right in place. There was slight ptosis of both lids, with possible weakness of upward gaze.

Forty-eight hours after the operation at 5 P.M., the rectal temperature, respiratory rate and heart rate were normal again.

Three days after the operation, the torticollis was only slight and the tremor had disappeared. The eye-lids were still heavy, and tended to droop. There was still a proclivity for circling to the right. The animal's general activity was less than normal.

November 4, 1949, 25 days after the unilateral operation, the animal was sacrificed and the brain was prepared for microscopic study as before.

Location of lesions and degeneration (figs. 12–15). As in monkey no. 3, the needle was directed at a 15° angle from the vertical, but only on the left side. It reached the subthalamus at caudal mammillary body level and entered the midbrain at the medial border of the capsule of the red nucleus, involving the oculomotor nerve roots on the left.

Hypothalamus. This area escaped injury.

Subthamamus. The caudal end of the thalamic fasciculus is damaged on the left, along with fibers of the pallido-hypothalamic tract. The substantia nigra shows some degeneration bilaterally.

Midbrain. The lesion includes the medial tip of the capsule of the red nucleus on the left. The interstitial nucleus of the medial longitudinal fasciculus is destroyed on the left, with degeneration of the fibers of the fasciculus caudally through the pons as far as sections are available. The oculomotor nerve roots on the left are partially involved.

At the midbrain-pons junction there is also a small lesion of the pontine nuclei on the left near the midline with degeneration of a few fibers arching towards the lateral part of the deep mesencephalic nucleus.

The substantia nigra is slightly degenerated bilaterally. None of the fibers ventral to the red nucleus are injured.

Basal ganglia. No damage is evident.

DISCUSSION

Somnolent syndrome

Posterior hypothalamo-tegmental fibers (ventral part). In the brain sections of the three somnolent monkeys no. 1, no. 2, no. 3 described in the present paper, there is evidence to support Ranson's hypothesis that descending fibers from the lateral hypothalamus into the midbrain tegmentum are an efferent link in the chain of neurons related to maintenance of the waking state. In all three of these somnolent or drowsy monkeys, following either unilateral or bilateral hypothalamic lesions, a well-degenerated tract can be traced caudally from the lesion on the same side. This myelinated tract is situated lateral to the fornix at caudal tuber level and dorsolateral to the fornix at mammillary body level; it is flattened dorso-medially and ventrolaterally and resembles an inverted comma in coronal sections (Morgan, '27). As it approaches the level of the oculomotor nerve roots, the fibers spread out between the red nucleus and the mediocaudal end of the substantia nigra to disappear between the emerging oculomotor roots in the region of the ventral part of the deep mesencephalic nucleus (Crosby and Woodburne, '43). Because of the slight separation of the degenerated descending fibers within the bundle, it is not impossible that ascending fibers showing no degeneration may also be present. This possibility might provide a basis for Nauta's ('46) theory of a midbrain waking center with activity dependent upon ascending fibers.

The cells of origin for these degenerated fibers probably lie rostral to the lesion, since the degeneration occurred caudal to the lesion. Although the exact location of the neuron bodies is not ascertained in this study, the medial hypothalamic nuclei provide a possibility which is documented by the observations of Crosby and Woodburne ('51), who located the

cells of origin of the posterior hypothalamo-tegmental tract in the ventromedial and posterior hypothalamic nuclei. In location, this degenerated tract corresponds to the fibers which Crosby and Woodburne ('51) termed the posterior part of the hypothalamo-tegmental system. A portion of the anterior part of this system is also degenerated in monkey no. 1.

There is circumstantial evidence in the monkeys of the present series that the most lateral fibers of this degenerated bundle found in the lateral hypothalamic area have their origin in either the globus pallidus, the subthalamic nucleus, or in both, because these fibers pass through the medial tip of the subthalamic nucleus. This agrees in part with the description of Whittier and Mettler ('49a) of fibers from the globus pallidus, ending ventral to the red nucleus in the ventral tegmental area of Tsai (Crosby and Woodburne, '43), which they referred to as the pallido-subrubral tract, a component of the lenticular fasciculus. Glees and Wall ('46) also suggested that the subthalamic nucleus projects onto a nucleus dorsomedial to the substantia nigra.

Correlation of sleep syndrome with degeneration of fibers. In the present series of experiments, there is evidence that the degree of somnolence varies with the extent of degeneration of the ventral part of the posterior hypothalamo-tegmental system of fibers. In monkey no. 1 (figs. 1–6), the somnolence lasted 6 days and drowsiness continued until the 16th post-operative day. Both lateral hypothalamic areas were damaged at infundibular and at tuber levels so as to include the above mentioned descending fiber bundle. On the left, the fibers could not be traced because the lesion continued caudally to the red nucleus levels.

In monkey no. 2 (figs. 7–11), there was a trace of somnolence for 5 days, but only when the animal was isolated from the other monkeys. Drowsiness persisted until the 10th post-operative day. The lateral hypothalamic area was damaged only on the right at tuber and at mammillary body levels, with degeneration of the ventral part of the posterior hypothalamo-tegmental fibers on that side.

In monkey no. 3, there was only a 24-hour period of som-
nolence following a right unilateral operation. However,
drowsiness persisted for two and 8 days, respectively, fol-
lowing two successive left unilateral operations. The sections
show a minimal subthalamic lesion on the left at infundibular
levels, causing slight damage to the afore-mentioned lateral
fibers of the posterior hypothalamo-tegmental tract; on the
right, the lateral part of the tract also shows degeneration
as a result of damage to the tegmentum at the rostral end
of the midbrain.

Somatic features of somnolence syndrome. The somnolent
or drowsy syndrome, as demonstrated in the present study,
combines to greater or lesser degrees a number of somatic
and visceral features which are the antagonist (Hess, '32)
to those present in the orthosympathetic responses charac-
terizing the normal monkey. The somatic components (Hin-
sey, '40) to be noted are: a deficiency in spontaneous move-
ments necessary for locomotion, for feeding, for vocalization
and for facial expression; a tendency to retain, for an in-
definite time, unusual positions (which are cataleptic in
character) such as a sitting posture with the trunk, neck and
limbs in extreme flexion; and a lack of awareness of the
environment, except when maximal stimuli are applied, im-
plying that there is an increased threshold for response to
both internal and external stimuli.

Somatic changes were most severe immediately post-opera-
tively. The order of duration of effects, following bilateral
lateral hypothalamic lesions in monkey no. 1, was as fol-
lows:

> Catatonia 3–6 days
> Inactivity 7–14 days (refractory after the first response)
> > First opened eyes and lifted head in response to
> > noise, 7 days
> > First cried and exhibited organized kicking in re-
> > sponse to being held supine, 8 days
> Anorexia 7–14 days
> > Spoon feeding required, accompanied by body tremor
> > while held, 7 days
> > Spoon feeding supplement 8–14 days

Bowed posture 14 days

Apathy 7–17 days (docility thereafter)

    Response to fear by drawing back from stimulus 17

      days.

Visceral features of somnolence syndrome (table 1). Among the visceral components of the pattern observed are: a sharp decrease in rectal temperature, ranging from 1–5°C. (Ranson, '40); a tendency to diminish respiration and heart rate, the latter obtained less consistently; and constriction of the pupils, although this sign was frequently masked by direct damage of the constrictor fibers in the emerging oculomotor nerve roots. Third nerve damage and irritation may also account for the occasional lateral strabismus or nystagmus respectively.

Vegetative changes reached the lowest level at 14 days. The order of return of visceral functions, following bilateral lateral hypothalamic lesions in monkey no. 1, were as follows:

    Heart rate [6] — 75% normal on 17th day

    Respiratory rate [6] — 50% normal on 17th day

    Rectal temperature [6] — 17% normal on 17th day

    Body weight — gradual rehydration after 14th day

    Body immunity — less susceptible to infection after 14th

      day.

For animals with unilateral lesions, the effects were much the same, but were less severe; return to normal occurred in half the time required for recovery from a bilateral lesion (monkey no. 2). Following an incomplete unilateral lesion, still less time was required (monkey no. 3). In monkey no. 4 with a small unilateral tegmental lesion, the vegetative changes had disappeared 24 hours post-operatively.

[6] The per cent normal return for vegetative changes was obtained by the following method:

    N = Normal record of heart rate, respiratory rate or rectal tempera-

      ture before operation

    L = Lowest record following operation

    F = Final record of recovery

    T = Total difference between the normal and the lowest readings

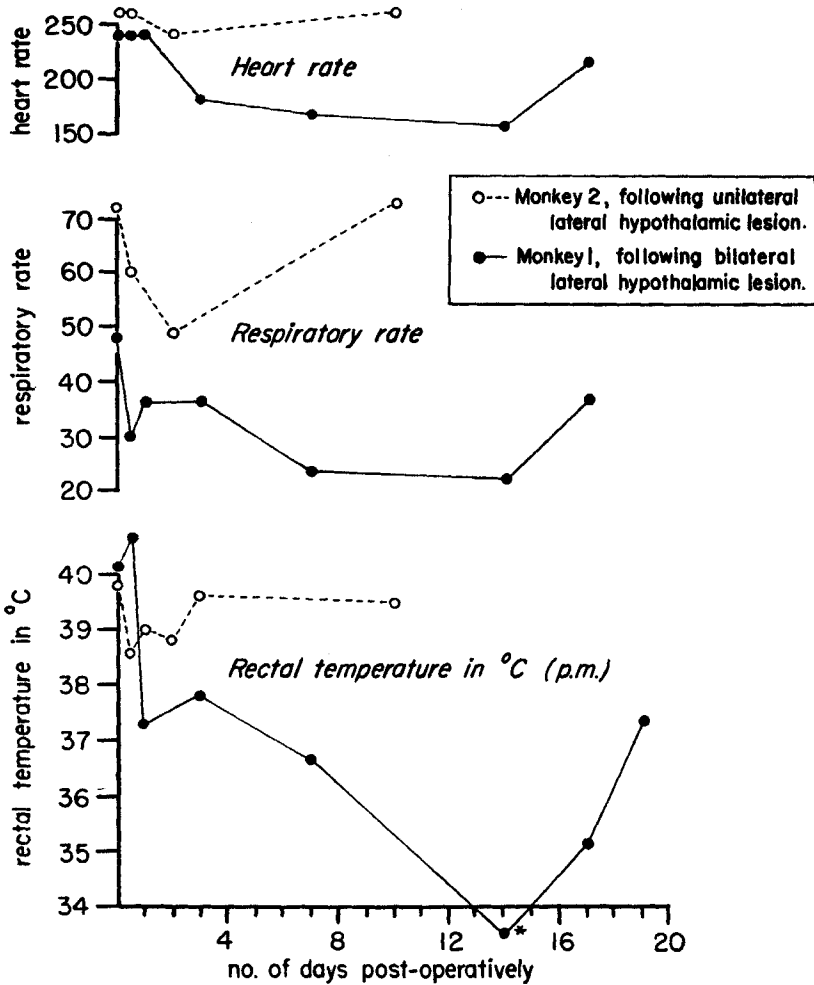   R = Return from the lowest to the final reading

      $T = N - L$ $R = F - L$ $\% N = R/T \times 100$

TABLE 1

A comparison of diurnal changes in rectal temperature, respiratory rate and heart rate following lateral hypothalamic lesions: monkey no. 1 has bilateral lesions and monkey no. 2 has a unilateral lesion

Note: Monkey no. 1 began feeding himself on the 7th day, whereas monkey no. 2 never had to be spoon-fed. In both cases, somatic activity, as exemplified by self-feeding, had resumed before the vegetative changes had reached their lowest.

* On the 14th day the rectal temperature in monkey no. 1 was below the minimal thermometer reading of 34°C.

Torticollis and circling movements

Lesion. In monkey no. 4 there was no somnolent period. The lesion avoided the lateral hypothalamic area as well as the ventral tegmental portion of the midbrain. Damage was limited to the left midline portion of the midbrain, including the interstitial nucleus of the medial longitudinal fasciculus, the medial tip of the capsule of the red nucleus and the oculomotor nerve roots (figs. 12–15).

Somatic features. Respiration. Because breathing was interrupted at inspiration, while the lesion was being made, it may be argued that the initial momentary stimulation of the medial longitudinal fasciculus unilaterally may be responsible for contraction of the inspiratory muscles during the normal inspiration of the macaque, since little else was damaged.

Torticollis and circling. The degeneration resulting from the lesion of the medial longitudinal fasciculus on the same side may be responsible for the torticollis to the opposite side, which was accompanied by circling movements to that side when the animal became excited. One may suppose that the excitation of the animal caused by staring at him effected stimulation of the intact right medial longitudinal fasciculus. Ingram and Ranson ('32) obtained circling and torticollis in cats having similar unilateral lesions.

Tremor. A fine bilateral tremor, especially marked on the side contralateral to the lesion, was present immediately following the operation but disappeared within two days. It is of interest that the rectal temperature was subnormal for the two days during which the tremor was evident. Ward, McCulloch and Magoun ('48) produced an alternating tremor at rest in monkeys having bilateral midline tegmental lesions.

SUMMARY

Somnolence syndrome

Anatomical findings. 1. There is a moderately myelinated descending path extending from the caudal hypothalamus to

the midbrain tegmentum, passing through the lateral hypo-
thalamic area and terminating at the level of the third nerve
roots in the ventral part of the deep mesencephalic nucleus.
It can be degenerated by a small lesion of the lateral hypo-
thalamic area at tuber and at mammillary body levels or more
caudally along its course into the rostral part of the midbrain
tegmentum. In location it corresponds to the ventral part of
the posterior hypothalamo-tegmental fibers and to a few of
the anterior hypothalamo-tegmental fibers described by Crosby
and Woodburne ('51).

2. The cells of origin for this path cannot be ascertained
from the present study, although the primary origin for the
path is probably in one or more of the following hypothal-
amic nuclei: ventromedial and posterior hypothalamic nuclei
(Crosby and Woodburne, '51). A second possible source for
the most lateral fibers of the bundle is the globus pallidus
(Whittier and Mettler, '49a), or, less likely, the subthalamic
nucleus (Glees and Wall, '46).

3. The observed slight separation of the degenerated fibers
in the bundle gives rise to the possibility of ascending fibers
through this region.

4. A positive correlation was found between the severity
of the sleep syndrome and the degree of damage to the above
mentioned fibers.

Physiological findings. 1. Depending upon the size of the
lesions, there was a corresponding decrease in those responses
to internal and external stimuli which were subject to obser-
vation: unilateral lesions produced maximal effects up to
48 hours post-operatively; bilateral lesions produced maximal
effects up to 14 days post-operatively.

2. Elements in the behavior that correlated particularly
well may be listed as follows: (1) Those in response to in-
ternal stimuli: a fixed foetal posture, reduced voluntary
changes in body position and reduced spontaneous activity
associated with hunger. (2) Those in response to external
stimuli either auditory (i.e., noises of various sorts), tactile

(i.e., blowing into the animal's face), visual (i.e., food, other monkeys and human beings) or olfactory (i.e., food): diminution of startle response, diminution of food-seeking and chewing responses and diminution of emotional responses of aggression.

3. The difference between the drowsy and somnolent states was one of degree. Response to external and internal stimuli during the somnolent period occurred only after maximal stimuli and was very momentary.

4. Depending upon the extent of the lesion, the monkey would pass through a short somnolent period and then an extended drowsy period until he again appeared normal. With unilateral lesions, the somnolent period was either omitted or shortened.

5. Somatic effects were immediate in appearance after the lesions, whereas vegetative responses such as heart rate, respiratory rate and rectal temperature, although also affected immediately, achieved their maximal change only after a partial return to normal of the somatic features. After an approach to normal of the somatic and vegetative features, there remained a personality change, for the animal was noticeably docile.

Torticollis and circling movements

Anatomical and physiological findings. 1. A lesion limited to the left midline portion of the midbrain tegmentum, including the interstitial nucleus of the medial longitudinal fasciculus, the medial tip of the red nucleus, and the oculomotor nerve roots, resulted in torticollis and circling movements to the opposite side, accompanied by a fine bilateral tremor especially marked on the contralateral side.

2. With this lesion there was no evidence of somnolence syndrome complications.

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ABBREVIATIONS

aq., aqueduct
C.G., central gray
C.N., caudate nucleus
C.P., cerebral peduncle
D.B.C., decussation of the brachium
    conjunctivum
D.T., dorsal thalamus
F., fornix
I.C., internal capsule
I.N., interstitial nucleus of the medial
    longitudinal fasciculus
I-P.N., interpeduncular nucleus
M., mammillary body
M.L.F., medial longitudinal fasciculus
M-T.T., mammillo-thalamic tract

O.T., optic tract
P-H.T., pallido-hypothalamic tract
P.H-T.T, posterior hypothalamo-teg-
    mental tract, ventral part
P.T., pyramidal tract
R.N., red nucleus
S-M.C., supramammillary commissure
S.N., substantia nigra
S-T.N., subthalamic nucleus
T., tuber cinereum
V.D.M.N., Ventral part of the deep
    mesencephalic nucleus
III N., nucleus of the oculomotor nerve
III R., oculomotor nerve roots
III v., third ventricle

PLATE 1

EXPLANATION OF FIGURES

Figures 1–4 are photomicrographs of 25 μ thick coronal sections, from the brain of monkey no. 1, which were prepared by the Swank-Davenport modification of the Marchi technique for staining degenerated myelinated fibers. Figures 5–6 are photographs of monkey no. 1 taken three days after the third operation.

1 Level of the tuber, showing bilateral lateral hypothalamic lesions.

2 Level of the mammillary bodies, showing the hypothalamic lesion on the left side and degeneration of the hypothalamo-tegmental fibers on the right side.

3 Level of the diencephalic-mesencephalic junction, showing the lesion on the left side and degeneration of the ventral part of the posterior hypothalamo-tegmental fibers on the right side.

4 Level of the oculomotor nerve roots, showing the caudal end of the lesion on the left side and the disappearance of the hypothalamo-tegmental fibers in the ventral part of the deep mesencephalic nucleus on the right side.

5 Cataleptic pose.
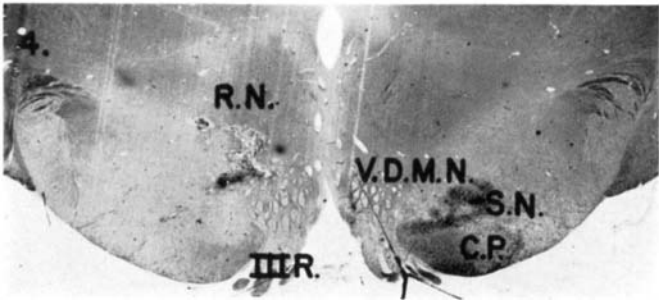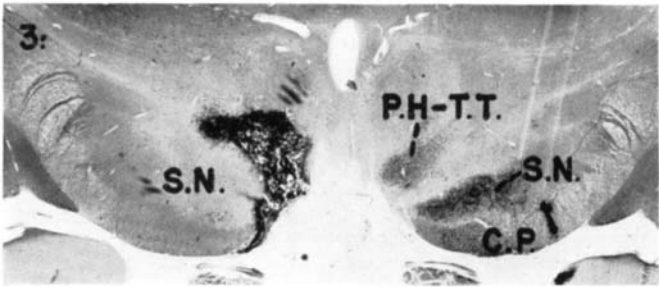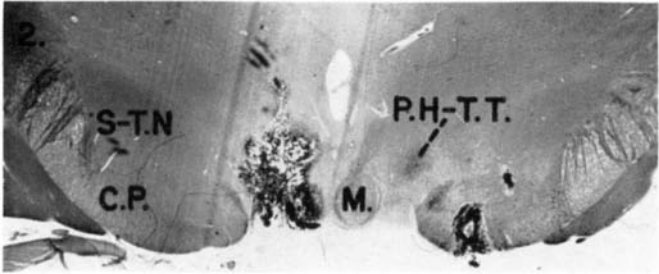
6 Foetal posture assumed throughout the somnolent period.

PLATE 2

Figures 7–10 are photomicrographs of 25 μ thick coronal sections, from the brain of monkey no. 2, which were prepared by the Swank-Davenport modification of the Marchi technique for staining degenerated myelinated fibers.

7   Level of the tuber, showing a right unilateral lesion in the lateral hypothalamus.

8   Level of the mammillary bodies, showing the right unilateral hypothalamic lesion.

9   Level of the diencephalic-mesencephalic junction, showing degeneration of the ventral part of the posterior hypothalamo-tegmental fibers on the right side.

10 Level of the oculomotor nerve roots, showing the disappearance of the hypothalamo-tegmental fibers in the ventral part of the deep mesencephalic nucleus on the right side.

11 Photograph of monkey no. 2 during the somnolent state, taken 4 days after operation, while his arms were held from behind.
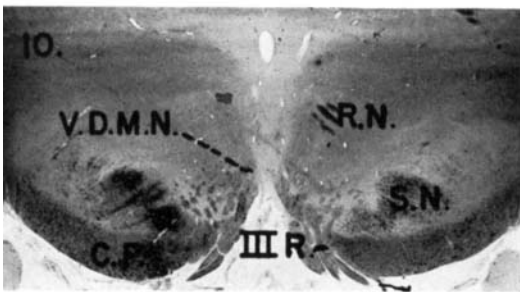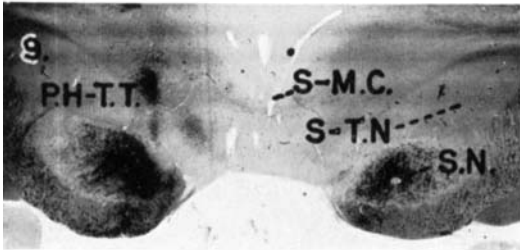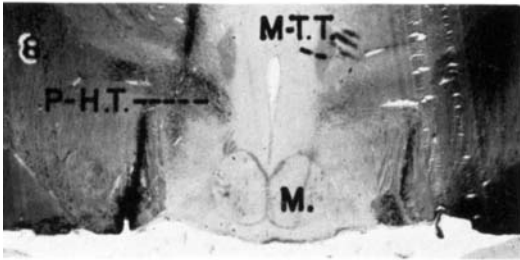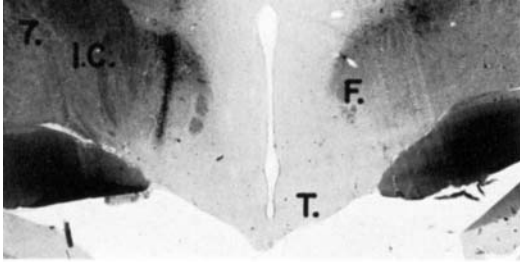
Figures 12–15 are photomicrographs of 25 μ thick coronal sections, from the brain of monkey no. 4, which were prepared by the Swank-Davenport modification of the Marchi technique for staining degenerated myelinated fibers.

12   Level of the oculomotor nerve roots, showing the left unilateral lesion through the capsule of the red nucleus.

13   Level of the midbrain-pons junction, showing the left unilateral lesion through the interpeduncular nucleus and degeneration of the medial longitudinal fasciculus.

14   Level of the midbrain-pons, showing the left unilateral lesion through the interpeduncular nucleus and degeneration of the medial longitudinal fasciculus.

15   Level of the midbrain-pons-medulla junction, showing the degeneration of the medial longitudinal fasciculus.