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I. INTRODUCTION

Detailed study of highest level epileptic seizures (petit mal epilepsy) by Dr. Penfield and his co-workers has yielded considerable evidence of a localizing nature in this disorder.

The characteristic feature of a highest level seizure is initial loss of consciousness. There may be little or no bodily manifestation of change. If there is any outward evidence, it may only be a staring expression of the eyes, or the eyes may turn upward, or blinking of the eyes may occur rhythmically. Movement of the extremities may be momentarily retarded or arrested, jerking movements of the arms may occur, or the patient may fall to the ground due to a sudden loss of postural control. The patient does not have any memory of the attack.

Such clinical evidence indicates a primary loss of consciousness with somatic symptoms which are not characteristic of cortical excitation but which are more readily associated with a subcortical discharge.

Changes of consciousness are also seen following lesions of the mesial wall of the diencephalon without clinical evidence of paralysis of corticospinal or other cortical mechanisms. Such patients may be unconscious for long periods, although all extremities move in readjustments of posture or when they

receive nociceptive stimulation (Penfield and Jasper, 1947).

Such evidence indicates that in highest level seizures there is a focal neuronal discharge which paralyses ganglion cells in that region of the brain which is most essential to the existence of consciousness, this region apparently being in the diencephalon and mesencephalon.

Electroencephalographic evidence supports such an assumption. The loss of consciousness associated with these seizures is accompanied by a generalised bilaterally synchronous 3 per second wave and spike rhythm. The spike component is highly variable and may in fact disappear for a time during the seizure. The wave and spike disturbance involves the entire cortex and begins and ends suddenly as though some centrally placed switch were turned on and off. (Jasper and Fortuyn, 1947). Direct observations,using pharyngeal electrodes, support the conception that basal areas of the brain (diencephalic) participate in the wave and spike discharge, and may be their site of onset (Jasper, 1941).

Experiments with anaesthetised cats designed to clarify the functional anatomical components involved in petit mal epilepsy demonstrated that all the features of the electro-encephalogram of patients with highest level seizures could be reproduced by rhythmic electrical stimulation with brief shocks in the anteromedial region of the thalamus (Jasper and Fortuyn, 1947).

Similar thalamic stimulation in the unanaesthetised cat produced momentary arrest of spontaneous activity and in one instance a seizure closely resembling petit mal epilepsy (Jasper and Hunter, 1948).

Such evidence implicates the diencephalon as playing an important part in highest level seizures and therefore in consciousness itself.

With the development of the stereotaxic instrument for operations on the human brain, localised surgical therapy in the diencephalon becomes possible in man (Speigel, Wycis, Marks and Lee, 1947).

In this investigation lesions in the diencephalon of man, and experimental ablations in the diencephalon of the cat and the monkey (Macacus rhesus) were chosen for study in the hope of clarifying the function of this region particularly in its relation to consciousness.

II. ANATOMY

The diencephalon encloses the third ventricle of the brain forming its lateral walls and floor. It is composed of the epithalamus, the thalamus, the ventral thalamus and the hypothalamus.

Phylogenetically, all these structures may be considered older than the more recently acquired areas of the cortex but the epithalamus and hypothalamus (with the possible exception of the medial mammillary nucleus) appear older than the thalamus in that they retain much of their original form in the course of evolution. The thalamus, however, shows a progressive development in keeping with the cortical development of higher animals (Smith, 1910).

The Epithalamus

The epithalamus includes the pineal body, stria medullaris and the habenular nuclei, located on the dorso-medial aspect of the thalamus. The stria medullaris, a band of fibres arising in the olfactory centers on the basal surface of the hemisphere and forming a semicircle around the dorsum of the thalamus, terminates in the habenular nuclei. Fibres arising in the habenular ganglion pass ventrally through the thalamus as the habenulo-peduncular tract to the interpeduncular ganglion. This

system, which is more highly developed in lower animals, is apparently part of an arc for olfactory reflexes.

The pineal body is believed to be the rudimentary remnant of a special dorsal sense organ seen in some primitive vertebrates.

The Thalamus

The two thalami form the lateral walls of the third ventricle. Each is an ovoid mass placed obliquely across the cerebral peduncles. The anterior limit of the thalamus is more medial than its posterior extent and protrudes forwards as the tuberculum comprising the anterior nuclear group. The posterior extremity known as the pulvinar is wider than the tuberculum and from its medial surface projects the medial geniculate body.

For purposes of description the thalamus is considered in six planes: dorsal and ventral, medial and lateral, anterior and posterior. The dorsal surface is free but in relation to the fornix and corpus callosum, the ventral surface lies in relation to the tegmentum of the mesencephalon. Medially the thalamus forms the wall of the third ventricle and in lower animals a bridge of gray matter and fibres bridges across the third ventricle as the massa intermedia. This structure is absent in about 20 per cent of human brains.

Laterally the thalamus is bordered by the internal capsule from the lenticular nucleus. Anteriorly the tuberculum

forms the posterior wall of the foramen of Munro and posteriorly the pulvinar is in close relation to the brachia of the corpora quadrigemina and posterior columns of the fornix.

A thin layer of fibres, the internal medullary lamina, divides the thalamus into a medial and lateral nuclear group. Anteriorly, at the beginning of the tuberculum,the internal medullary lamina splits to enclose the anterior nuclear group. The lateral boundary of the thalamus is surrounded by the external medullary lamina. In the following account the terminology of Walker (1938) has been adopted. Anatomically, there are six major nuclear masses: 1) nuclei of the midline, 2) anterior, 3) medial, 4) lateral, 5) ventral, 6) pulvinar (including medial and lateral geniculate bodies).

According to Walker's studies made by cortical ablation and studying the retrograde Nissl degeneration of the primate thalamic nuclei,he concluded that the main anatomical organisation and connections are as follows:

Nuclei with subcortical connections. This group is made up of nuclei with entirely subcortical connections restricted to the diencephalon and corpus striatum, and includes the nuclei of the midline, the intralaminar nuclei (those nuclei lying within the fibres of the internal medullary lamina) and the nucleus ventralis anterior.

Cortical relay nuclei. This group includes those nuclei which receive fibres from the great sensory systems and project in turn to the primary motor and sensory regions of the cerebral cortex. These include the nucleus ventralis lateralis, nucleus ventralis posterior, the anterior nuclei, and the geniculate bodies.

Association nuclei. Included in this group are those which receive no fibres from the ascending systems but have numerous connections with other diencephalic nuclei, and project to association areas of the cerebral cortex, e.g. parietal and prefrontal. These include the nucleus medialis dorsalis, nucleus lateralis dorsalis, nucleus lateralis posterior and the pulvinar nuclei except for a small medial part.

Seven great sensory systems play upon the thalamus. Four are concerned with the special senses - olfactory, visual, auditory and gustatory - and three are related to somatic sensation - the spinothalamic and dorsal secondary trigeminal tracts, the medial lemniscus and ventral secondary trigeminal tract, and the brachium conjunctivum. Less well understood are the ascending fibre systems from the mesencephalon and hypothalamus chief of which are the mammillothalamic tract and the periventricular fibre system. These tracts may well relay from the hypothalamus visceral and somatic sensory impressions from many visceral sources (Papez, 1937).

Each of the cortical relay and association nuclei projects to a local area of the cortex, which in turn has corticothalamic connections. For example, the nucleus dorsalis medialis projects to areas 9 and 10 of the prefrontal agranular cortex, and this area in turn has corticothalamic connections with Nucleus dorsalis medialis.

All thalamic nuclei appear to have intrathalamic internuclear connections. Little is known of striatothalamic pathways, but the thalamic fasciculus appears to connect the globus pallidus with the nucleus ventralis anterior.

Thus, for example, visual, tactile and auditory impulses are relayed in the thalamus via the lateral geniculate bodies, the nucleus ventralis lateralis and medial geniculate bodies to the occipital, postcentral and temporal cortex respectively.

Thus, the function of the thalamus from a purely anatomical viewpoint would appear to be one of integration and synthesis of all forms of sensory impressions. From here such a sensory synthesis would have ready access to all parts of the cortex and corticothalamic and intrathalamic connections would make possible a complexity of integration limited only by the degree of development of the central nervous system itself.

The Ventral Thalamus

The ventral thalamus, or so-called subthalamus, lies between the tegmentum of the midbrain and dorsal thalamus. Included in this structure are the fields of Forel, the subthalamic nucleus or corpus Luysii, and projection fibres from the substantia nigra and red nuclei. The fields of Forel are an area of fibre pathways from the globus pallidus and it is from here that the thalamic fasciculus is formed and passes to the nucleus ventralis anterior. The subthalamic nucleus also receives fibres from the globus pallidus and forms an important part of the descending pathways of the corpus striatum.

The Hypothalamus

The hypothalamus is a phylogenetically old constellation of nuclei lying between the oculomotor nerves but above the optic chiasm and sella turcica. It appears to be the centre for the integration of visceral functions involving the autonomic nervous system.

The principal hypothalamic nuclei may be divided into five main divisions as follows:

1. Periventricular region

These small cells,almost devoid of cytoplasm,lie scattered around the floor of the third ventricle and form poorly distinguished nuclear groups. They form the substantia

grisea centralis and it is with these cells that the peri-ventricular fibre system forms a connection to the midline thalamic nuclei.

2. Anterior group.

The anterior group includes the paraventricular or filiform nucleus and the supraoptic nuclei. The supra-optic nuclei lie below the paraventricular nuclei but just above the anterior end of the optic tract. This nucleus gives rise to the supra-optico-hypophyseal tract passing via the pituitary stalk to the hypophysis. Degenerative changes occur in this nucleus after destruction of the posterior lobe of the pituitary.

3. Lateral group.

The lateral group includes the lateral area of the tuber cinereum and the lateral tuber nuclei.

4. Middle group.

Included in the middle group are the ventromedial hypothalamic nucleus, the dorsomedial hypothalamic nucleus and the medial tuber nuclei.

5. The posterior group.

The posterior group is made up of the posterior hypo-thalamic area and the mammillary body which is composed of three discrete nuclear masses: the medial mammillary nucleus, the lateral mammillary nucleus and the nucleus intercalatus.

The largest cell group, the medial mammillary nucleus , becomes highly developed in man and the higher primates.

The mammillary bodies are of special interest in relation to the diencephalon as a whole since they give rise to the main two-way fibre system connecting hypothalamus with thalamus (Clark and Boggan, 1933b). This fibre tract appears to terminate for the most part in the anteromedial thalamic nuclei, although some fibres pass to the anteroventral and anterodorsal thalamic nuclei. The mammillary bodies are the principal end station of the fornix fibres from the hippocampus. A descending fibre tract of uncertain destination passes from the mammillary region via the posterolateral hypothalamus to the tegmentum.

III. PHYSIOLOGY

The diencephalon, lying as it does in the centre and base of the brain, comprises the most inaccessible structures of that organ. For this reason, accurate evaluation of its function presents many technical difficulties which may account for the obscurity surrounding much of its function.

Information gained concerning diencephalic function has been achieved by clinical observation of destructive lesions and epileptic seizures involving this region in man, by diencephalic ablation and stimulation in experimental animals and by electroencephalographic studies in man and in experimental animals.

Diencephalic Lesions in Man

The commonest diencephalic lesions in man are on a vascular basis and involve the thalamus. The largest sources of blood to the thalamus are the posterior cerebral artery and its branches. The thalamoperforating arteries supply the anterior portion of the thalamus. The thalamogeniculate arteries supply the posterolateral thalamus. The remaining portions of the thalamus receive their supply from the anterior and posterior choroidal arteries and the lenticulo-optic artery.

The classical thalamic syndrome (Dejerin and Roussy, 1906) is caused by obstruction of the thalamogeniculate

artery. The significant symptoms in this disorder are disturbances of superficial and deep sensibility varying from fleeting hemianaesthesia and hemiastereognosis to dysaesthesia. Frequently associated with these disturbances are severe,agonizing and persistent intolerable pains on the affected side. The primary abnormality is damage to the anterior portion of the pulvinar and the nucleus ventralis posterior and their related fibre tracts.

Thrombosis of the thalamoperforating artery produces destruction largely confined to the nucleus ventralis lateralis. Ataxia and abnormal motor phenomena are the characteristic disturbances of this syndrome and appear to be related to the damage of the terminations of the brachium conjunctivum.

Tumours not uncommonly involve the diencephalon, but it is unfortunate that small tumours with well defined localisation have rarely been reported.

Sinkler (1893) reported a tumour the size of a hen's egg in the posterior part of the thalamus causing recurrent attacks of drowsiness, but the structures involved were inadequately described.

Mott and Barratt (1900) described a tumour involving the anterior thalamic nuclei, the patient exhibited drowsiness, sometimes falling asleep when taking food.

Weisenburg (1911) collected 27 cases of third ventricle tumours and added three cases of his own to this report. In

all cases there was inadequate pathological and clinical data. Drowsiness and attacks of unconsciousness, together with vasomotor changes were common disturbances. However, he was unable to exclude the effects of intracranial tension and concluded that "the occurrence of mental symptoms is dependent upon the compression of the cortex against the skull resulting from internal hydrocephalus".

Guillain, Bertrand and Périsson (1925) observed hypersomnolence in a case of tumour of the third ventricle, and Drennan (1929) reported unconsciousness and sudden death in two cases due to impacted cysts in the region of the foramina of Munro.

Fulton and Bailey (1929) in their excellent review of the literature pertaining to tumours in the region of the third ventricle and their relation to pathological sleep emphasised the importance of excluding intracranial tension before hypersomnia can be concluded as being of localising significance. Their impression was that a number of syndromes may be classified in tumours of this region depending upon the nature of the structural damage in the walls of the third ventricle. Their classification was as follows:

1. The infundibular syndrome (polyuria, adiposity).
2. The syndrome of the central gray matter around the posterior end of the third ventricle and aqueduct of Sylvius (hypersomnia).

3. The thalamic syndrome (central pain, painful hyperaesthesia).
4. The extrapyramidal syndrome (bradykinesis, rigidity).
5. The decerebrate syndrome (hypertonicity, Magnus and de Kleijn reflexes).
6. The syndrome of Perigaud (paralysis of conjugate vertical movement of the eyeballs).
7. The syndrome of the body of Luys (hemichorea).
8. The hypopituitary syndrome (infantilism, hypotrichosis lowered metabolism).

Glaser (1929) categorically stated in a discussion of tumours in the region of the third ventricle that "without doubt mental symptoms when they occur are the result of internal hydrocephalus". This statement, however, would not be in agreement with the studies of many others who conclude that hypersomnolence may occur with tumours in this region (Lhermitte, 1932; Dandy, 1933; Rinder and Cannon, 1933; Zeitlin and Lichenstein, 1937).

Smyth and Stern (1938) reported a case of a diffuse glioma of the massa intermedia with progressive drowsiness, confusion and dementia; speech, however, was not impaired.

Penfield (1938) in a discussion of consciousness stated that long-continued unconsciousness appears clinically in patients who have a lesion in an area above but not far removed from the midbrain and its vicinity.

Penfield and McEachern (1938) in a discussion of the syndrome of diencephalic tumour concluded that a pathological tendency to somnolence may appear when the lesion is in the vicinity of the head of the caudate and anterior thalamus, and if infiltration is wide the patient sinks into a continuing stupor. Loss of pain sensation and at times diffuse burning contralateral pain of the so-called thalamic type occurs with involvement of the thalamus. There may be a unilateral disturbance of sweating throughout the body, or other autonomic functions may be interfered with. Diabetes insipidus characterised by polydipsia and polyuria is produced by tumours involving the tuber cinereum either directly or by pressure.

Cairns, Oldfield, Pennybacker and Whitteridge (1941) reported an important case of what they termed "akinetic mutism" in a case of epidermoid cyst of the third ventricle. In this paper the case was reported in some detail in order to assist recognition of this clinical state and also to bring forward clinical evidence relative to the influence of the diencephalon on the cortex and on consciousness. No anatomical studies were made in this case but they concluded that total immobility and mutism may be associated with the pressure of a cyst of Rathke's pouch upon structures surrounding the third ventricle. The most profound manifestations were mutism, loss of feeling tone, loss of emotional expression, loss of spontaneous and voluntary movement and total incontinence of urine and faeces.

Ocular fixation and movement occurred in response to the movement of external objects and to sounds. There was a disturbance of consciousness at the highest level as evidenced by total amnesia, upon recovery, for the period of the episode.

Stern and Dancey (1942) reported a glioma of the diencephalon in a manic patient and concluded that the psychotic symptoms were related to the tumour. Shapiro (1948) observed severe intellectual deterioration in a thalamic tumour.

Dandy (1946) concluded from a series of tumour resections in the region of the third ventricle that there exists a specific area of the brain controlling consciousness. From the results of extensive resections of the brain, he stated that neither cerebral hemisphere above the basal ganglia plays any part in consciousness. He admitted that much of his postmortem study was inadequate but stated that "loss of consciousness probably therefore results either from direct trauma to the anterior part of the corpus striatum or from deprivation of its blood supply".

Other less direct evidence has been advanced in clinical studies related to diencephalic function. Alford (1932) observed a large series of patients exhibiting lesions in different parts of the brain for any changes in consciousness and emotion. In no lesion of the right hemisphere (in right handed persons) was any consistent disturbance in these two faculties observed. It was eminently in the right hemiplegias which generally arose from left capsular injuries that definite and permanent confusion of consciousness was found. He con-

cluded that an area somewhere in the left basal region of the brain is concerned with the maintenance of awareness.

Rowe (1935) from a study of two poorly localised tumours of the diencephalon and an exhaustive review of the literature concluded that "disturbances of sleep result from lesions of a rather diffuse cerebral correlating mechanism, which may lie in the medial thalamic nuclei, or from the interruption of a thalamo-periventricular-hypothalamico-mesencephalic chain of neurones conducting impulses to or from such a mechanism".

Laruelle (1936) concluded from pathological studies that what he termed the large cells of the substantia reticularis on either side of the foramen of Monro are presumably concerned with the function of sleep.

Stern (1939) reported a case of a man who became progressively drowsy, and gradually lost his speech. He did not use wrong words, nor was there any apparent difficulty in expression, it was simply that he spoke less and less. He became progressively slow in all his movements until finally he became completely inert. There was no tremor or paralysis of the limbs. Autopsy revealed a system degeneration of unknown aetiology with bilaterally symmetrical degeneration of both thalami which principally involved the medial nuclei, the anterior nuclei, the centromedian nuclei and the lateral nuclei. The hypothalamic nuclei were intact in this case, but there was cortical gliosis which was interpreted pathologically to be of more recent onset

than the thalamic degeneration.

Alpers (1940) described a case of dermoid cyst of the third ventricle associated with severe changes in personality and in mood. Histological studies revealed severe damage to the nuclei of the hypothalamus. There was also damage to the medial thalamus. The author concluded that the personality changes were due to the hypothalamic damage.

Cytological studies by the Vogts (1948) led them to conclude that in schizophrenia there were cell changes in the thalamus particularly in the dorsomedial nucleus. Morgan (1940) has reported cell changes in the hypothalamus in major psychoses.

In the clinical literature relating to the hypothalamus the disorders resulting from its injury may be classified into three groups other than those already described. These are hyperthermia, diabetes insipidus, and the adiposo-genital syndrome. The relation of these syndromes to hypothalamic damage is well established (Alpers, 1936; Clark, Beattie, Riddoch and Dott, 1938; Zimmerman, 1940)

Diencephalic Autonomic Epilepsy.

In 1929, Penfield described the first reported case of an epileptic discharge involving the diencephalon. The patient had repeated attacks in which there were mainly sympathetic phenomena consisting of tachycardia, flushing of face, slowing of respiration, lacrimation, diaphoresis, salivation, and

dilatation of pupils. Attacks of unconsciousness also occurred. Postmortem study revealed a pearly tumour compressing the mesial and anterior aspects of the thalamus on each side, there was some recent softening in the region of the anterior thalamic nuclei. It was concluded from this case that in the thalamus and not the hypothalamus was the highest representation of the vegetative nervous system.

Sjöquist (1941) has described a striking case of autonomic epilepsy in man associated with episodes of sham rage. The lesion lay deep in the right temporal lobe and caused marked distension of the third ventricle.

Penfield and Erickson (1941) have reported other cases of diencephalic autonomic epilepsy.

Aring and Engel (1945) reported another case under the title "Hypothalamic attacks with thalamic lesion". In this instance an 18 year old boy had recurrent attacks of coryza, chills, fever, nausea, vomiting, abdominal cramps, fluctuating hypertension, tachycardia and muscle cramps which began at five months. There were frequent episodes of unconsciousness. Pathological study revealed a cystic softening of the right dorsomedial nucleus just below the anterior nuclei, the internal medullary lamina and lateral nucleus of the thalamus. The hypothalamus was intact.

Diencephalic Studies on Experimental Animals

The literature on this subject is so vast that only a survey will be reviewed here.

Spiegel and Inaba (1927) made stab wounds in subcortical structures in rabbits and dogs and concluded that a sleepy state could be produced by thalamic damage. The hypothalamus did not appear to be damaged. Their lesions, however, owing to the limitations of the methods used, were poorly localised.

Ranson and his co-workers (Ranson and Ingram, 1932; Ingram, Barris and Ranson, 1936; Ranson, 1937; Ranson, 1939) in a comprehensive study of lesions in the hypothalamus in cats and monkeys concluded that somnolence and catalepsy can be produced in the cat by damage "to some structure or structures in the neighbourhood of the mammillary bodies, such as the posterior hypothalamic nucleus, the supramammillary area, the lateral hypothalamic area and the region just caudal to the mammillary bodies". A more specific localisation could not be given. In the monkey, Ranson (1939) concluded that "all the evidence from this series of experiments points to the lateral hypothalamic area as the region bilateral destruction of which leads to somnolence". Small lesions placed in the same area bilaterally cause marked disturbance in the regulation of body temperature.

Hess (1944, 1947) in his exhaustive studies of electrical stimulation in the diencephalon of the cat found that following stimulation of the lateral part of the massa intermedia in the region of the mammillothalamic tract the cat settled down to sleep. Stimulation of the ventral thalamus and hypothalamus produced marked autonomic changes including pupillary changes,

blood pressure variation and change in heart rate, and respiratory change. Following bilateral coagulation in the hypothalamus of the cat, Hess reported a relative poikilothermia, complete passivity and loss of spontaneous activity with partial restitution after eight days.

Hess also reported a state he termed adynamia with stimulation in the region of the mammillary body, the lateral hypothalamus and the ventral thalamus.

Harrison (1940a) was not able to produce somnolence in cats by a stimulating current. He reported somnolence and subnormal motor initiative without abnormal plasticity in cats with either hypothalamic or thalamic lesions. The hypothalamic lesions were located in the lateral hypothalamic area. The thalamic lesions disclosed extensive bilateral damage extending from the pulvinar to the anterior thalamic nuclei. From his studies Harrison concluded that when somnolence is produced by the passage of an electric current through the diencephalon, the somnolence is due to destruction and depression and not to stimulation. Clinical evidence, however, would not support this view as it is well known that an epileptic discharge can cause a temporary paralysis of neural function.

Miller (1942) in his comprehensive review of autonomic regulation in the diencephalon points out that "it is difficult to see how in placing his hypothalamic lesions with the Horsley-Clarke apparatus Ranson could avoid damaging sensory

pathways to or within the thalamus. Be this as it may extensive lesions made by Ranson in the monkey (thalamus) failed to produce somnolence".

Miller and Spiegel (1940) produced sleep and catatonia lasting several days by lesions in the ventral thalamus of the cat. The hypothalamus was intact. Other functions of the diencephalon have been well established in experimental animals. Isenschmidt and Krehl (1912) observed that section of the junction of the diencephalon with the mesencephalon in rabbits resulted in loss of temperature control. Isenschmidt and Schnitzler (1914) concluded that the region of the tuber cinereum is the most important area for temperature regulation in rabbits. Extensive studies in other animals indicate that lesions in the anterior hypothalamic area result in hyperthermia and ablations in the posterior area result in hypothermia (Barbour, 1921; Pinkston, Bard and Rioch, 1934; Ranson, Fischer and Ingram, 1937; Ranson, 1940; Clark, Magoun and Ranson, 1939a).

Clark, Magoun and Ranson (1939b) were unable to demonstrate any significant disturbance in temperature regulation following thalamic lesions in the cat mainly confined to the posterior and medial regions of the thalamus. The anterior nuclei, however, were not destroyed.

There is considerable evidence both direct and indirect obtained from experimental animals that the hypothalamus is related to emotion. Bard (1928) in his well-known work in sham rage in the cat concluded that the hypothalamic area was essential for this reaction. Fulton and Ingraham (1929) found increased activity and emotional disturbances following prechiasmal lesions in the cat. Further evidence has been provided by Masserman (1941) by direct stimulation of the hypothalamus.

Wyss (1944) has produced permanent deficits of motor activity by diencephalic lesions in the cat.

Patton, Ruch and Walker (1944) have produced loss of taste by lesions of the nucleus ventralis posteromedialis in the thalamus of monkeys. Walker (1940) has been unable to note any change in behaviour following lesions of the nucleus dorsalis medialis in monkeys.

Lashley and Sperry (1943) have severed the cortical connections of the anterior thalamic nuclei (anatomically classified as part of the rhinencephalon and therefore considered to be functionally related to smell) in rats and demonstrated conclusively that there is no loss of olfactory discrimination. The animals, however, had to be force fed for several days and did not attempt to open their feeding boxes for many days.

Hoff (1937) in a review of the neurogenic factor in relation to gastric erosion reported that Maurizio Schiff in 1845 observed that lesions of the optic thalami and cerebral peduncles often led to softening of the stomach or even acute perforations. Hoff, himself, concluded from his experimental studies and the observations of others that gastro-mucosal erosions were most constantly a development following lesions in the tuberal region of the hypothalamus.

Electroencephalography and the Diencephalon.

Lesions involving the diencephalon in man give rise characteristically to generalised slow rhythmic waves, often called delta waves, which can be recorded with the scalp electrodes of the electroencephalograph. The nature of this abnormally slow activity is of localising value provided increased intracranial pressure can be excluded as a cause where cortical pressure against the cranial vault may give rise to similar slow potential waves at a rate of 2 to 3 cycles per second (Walter, 1936).

Cobb (1945) described certain similarities of the delta rhythm in lesions of the diencephalon with the 3 per second slow waves seen in petit mal epilepsy. His study of a large series of tumours in this region led him to conclude that lesions in the diencephalon gave rise to delta activity which was independent of intracranial tension.

This view is shared by most investigators (Gibbs,Davis and Lennox, 1935; Lennox and Brady, 1946). Cobb felt that involvement of structures in the posterior end of the third ventricle was the common factor in his cases, although he admitted that there was insufficient data for accurate localisation.

Walter and Dovey (1944), in a study of tumours involving the diencephalic region, found that activity at about 6 cycles per second from the postcentral and parieto-temporal areas was the commonest feature. They pointed out the relation that these waves bear to those occurring just preceding or just following natural sleep. Kennard and Nims (1942) and Kennard (1943a) found that in monkeys "lesions of the thalamus alter the pattern of cortical EEGs in general, but most markedly in the postcentral areas". These changes were usually in the production of waves at 6 to 8 cycles per second as distinct from the normal 8 to 10 cycles per second.

Morison and Dempsey (1943) by electrical stimulation of the thalamus in the cat were able to elicit primary responses in different cortical areas when the corresponding thalamic nuclei were stimulated; for example, in areas 9 and 10 when the dorsomedial nucleus was stimulated.

Dusser de Barenne and McCulloch (1938) demonstrated thalamo-cortical relations by a similar method in which strychnine was injected into the sensory thalamic nuclei and recordings were made from the corresponding cortical area. The value of the localisation in their method is open to question because of the possibility of diffusion of the strychnine into neighbouring nuclei and the inadequate histological control. Similar criticism applies to the work

of Murphy and Gellhorn (1945) who have demonstrated many hypothalamo-thalamo-cortical mechanisms by the strychnin-ization technique. They concluded that the mammillary body has an intimate relation with the dorsomedial nucleus.

Jasper and Fortuyn (1947) made the following contributions by electrical stimulation of the medial thalamus of the anaesthetised cat with simultaneous electrocortigraphic recording.

1) Stimulation of the internal medullary lamina gave rise to a generalised cortical response, more marked in the frontal parts than in occipital areas.

2) The form of the response varied but in various areas "wave and spike" patterns appeared, a wave form characteristic of petit mal epilepsy.

3) Single stimuli would initiate activity similar to the normal "burst" activity of the cortex of the lightly anaesthetised cat.

4) Repeated stimuli would produce more regular responses until the spontaneous activity was replaced by the response to stimulation.

5) Repeated stimulation showed augmentation, that is they produced a longer response than the initial stimulus.

Jasper and Fortuyn concluded that their results confirmed the impression that the anatomical substratum of petit mal epilepsy involves a local area in the lamina medullaris interna of the thalamus.

Jasper and Hunter (1948) have produced states of arrested movement simulating petit mal seizures by implanting electrodes in the intralaminar region and stimulating this area in the unanaesthetised animal.

The aim of the present study is to observe behavioural and electrographic changes in man following lesions in this region of the diencephalon, and to compare these with similar data obtained from animals in which small ablations were made in the diencephalon, in an attempt to gain insight into some of the neural mechanisms related to highest level seizures and to consciousness.

IV. METHOD

In the study of diencephalic lesions in man the records of four cases of Professor Wilder Penfield were made available at his kind suggestion.

The author was able to examine clinically and to attend the operation of one patient, and in the other cases the data were gained from the hospital records and from the staff men connected with the cases. The author also prepared and studied the pathological material of these cases. The electroencephalographic interpretation of these cases was made from the reports of Dr.Herbert Jasper.

In the series of animal experiments 23 cats and 2 monkeys (Macacus rhesus) were used. The animal, following preoperative observation and recording of temperature, pulse and respiration, was anaesthetised with intraperitoneal nembutal (0.5 cc. per kg.). The head was shaved and six sterile dural screw electrodes were placed permanently in the skull in uniform frontal, temporal and occipital positions by means of a standard scalp marker. These permanent electrodes facilitated taking postoperative electroencephalograms without anaesthesia. (See Figs. 1 and 2.)

The animal was then placed in the Horsley-Clarke stereotaxic instrument and preoperative electroencephalograms recorded. The skull electrodes were connected with shielded wires to six channels of five-stage R.C. coupled amplifiers

Fig. 1

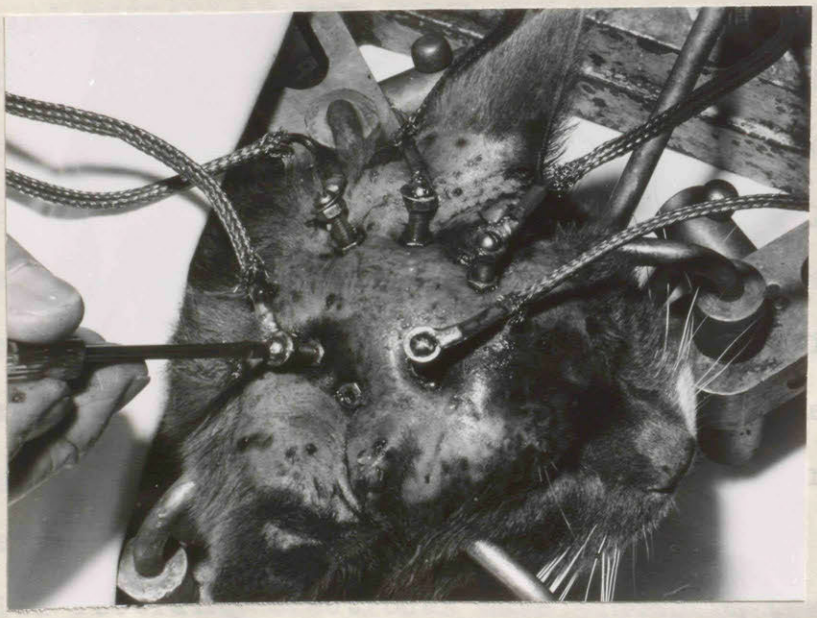


Fig. 2

Photographs illustrating the method used for obtaining electroencephalographic recordings in animals by means of screw electrode units inserted into the skull. The first figure shows the units permanently screwed into the skull. The second figure shows how the detachable shielded lead off wires are attached to these units.

and thence to a power amplifier driving a six pen Offner crystograph or (in later experiments) dynograph ink-writing units and to a triple-trace cathode-ray oscillograph.

Bipolar electrodes were used for the diencephalic ablations, the tips being separated by 1.5 to 2 mm. Two types of electrodes were used. The first type consisted of steel needles held in a heat resistant ceramic cylinder, sealed with cement and insulated to the tips with two coats of silicone insulating varnish (Dow Corning Corporation D.C. 996) and oven dried. The second type consisted of platinum wires sealed into pyrex capillary glass tubes and were found to be more satisfactory.

A midline trephination was performed under aseptic conditions and the needles were lowered into the area to be studied using coordinates modified from the atlas of Ingram, Hannet and Ranson (1932). In many experiments the final position of the electrodes was controlled by the electroencephalographic response following stimulation, e.g., stimulation of the dorsomedial nucleus produced a primary response in areas 9 and 10 of the cortex. For special localisation studies of the mammillary bodies and anterior nuclei recording electrodes were placed on the cingulate gyrus. This method of placement control was made at the suggestion of Dr. Jasper and Dr. Hunter from their unpublished work. Such electrographic control gave accurate placement within one millimeter. (See Fig.3) The stimulus was a

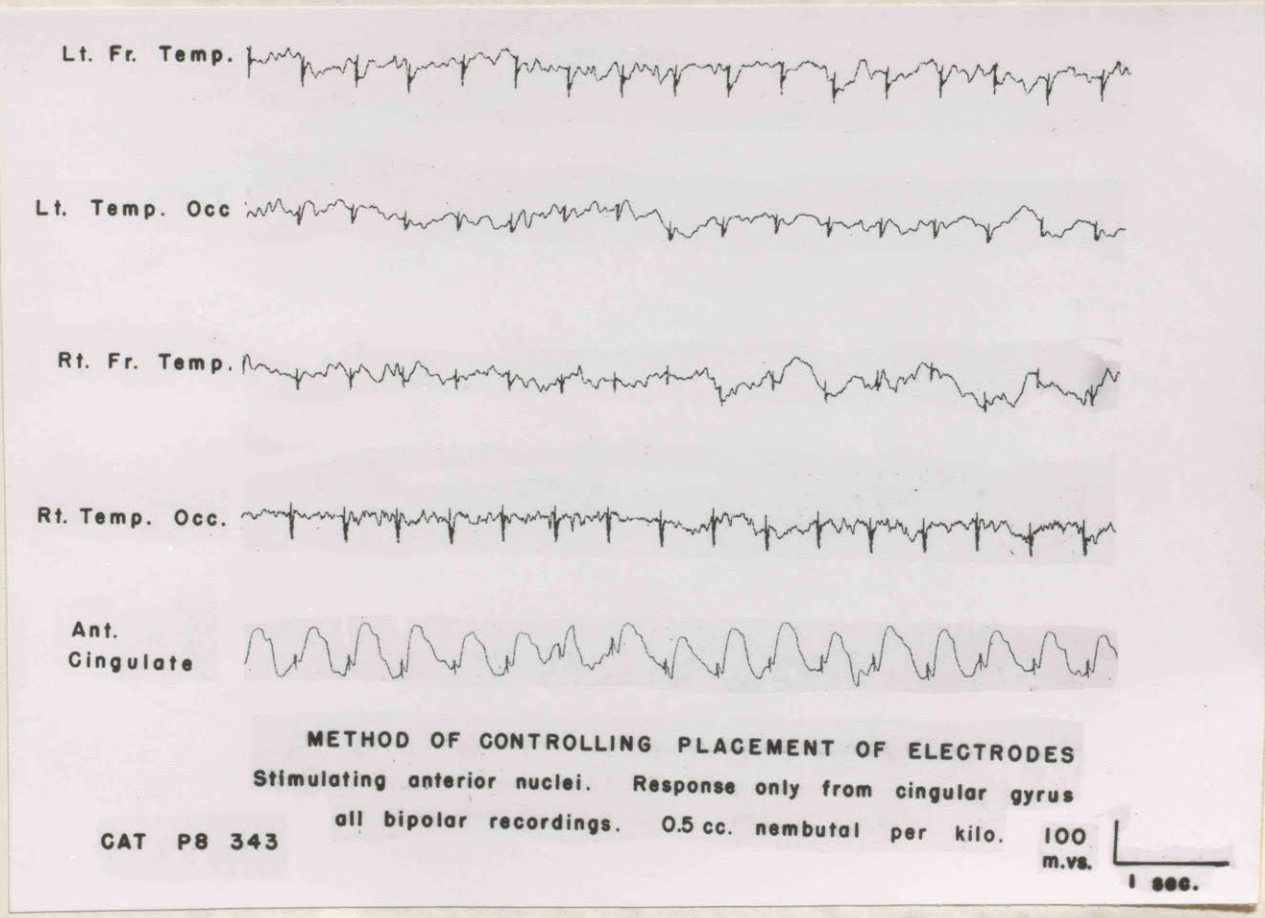

Lt. Fr. Temp.
Lt. Temp. Occ
Rt. Fr. Temp.
Rt. Temp. Occ.
Ant. Cingulate
METHOD OF CONTROLLING PLACEMENT OF ELECTRODES
Stimulating anterior nuclei. Response only from cingular gyrus
all bipolar recordings. 0.5 cc. nembutal per kilo.
CAT P8 343
100 m.vs.
1 sec.

Figure 3

condenser discharge of 1 or 2 milliseconds duration. The strength of the stimulus was regulated between 0 and 10 volts by means of a potentiometer. The frequency of the stimulus varied from less than 1 to 40 per second. The shock artefact was eliminated by leading the stimulus output to ground through a balancing potentiometer connected across the stimulus output.

With this apparatus three channels could be visualised on the cathode-ray screen and on the ink-writer at the same time.

Electrocardiographic records were made in several experiments before and after the ablations were made by connecting lead electrodes surrounded by a pad soaked in saline on both forepaws, and connecting these to one channel of the ink-writer. Thus, an electrocardiogram could be recorded simultaneously with the electroencephalogram.

Electrolytic ablations were made in the diencephalon by passing direct current through the bipolar electrodes from a constant current power supply, having a maximum output of 25 milliamperes. The current was independent of resistance from 0 to 25,000 ohms. A current of three milliamperes was passed for measured periods of time varying from one to three minutes. The polarity was then reversed and the procedure repeated. Both unilateral and bilateral lesions were made.

The postoperative behaviour, temperature, pulse, respiration and electroencephalogram were studied for periods varying from two to sixty-two days, the average period of study being ten days.

Animals with marked behavioural changes were studied with 16 mm. colour cinematographic records for exact comparison.

The animals were sacrificed by nembutal anaesthesia and perfusion of the brain through the carotid arteries with saline followed by an isotonic solution of formalin and gum-acacia (Koenig, Groat and Windle, 1945). The brain was then removed and placed in 10 per cent formalin. After fixation the blocks were embedded in paraffin and serial coronal sections were made (20 *mu* thick). Every fourth and fifth sections were stained for myelin (Weil, 1928) and with aniline-thionin for Nissl substance.

V. RESULTS

A. DIENCEPHALIC LESIONS IN MAN

Impaired Consciousness in 4 Cases of Diencephalic Damage.

Case G.K.

Haemorrhagic cyst of the right thalamus.

First Admission

G.K., a 17 year old boy, was referred by Dr. Thomas Hibbert, of Rochester, New Jersey, to Dr.Penfield's service for the first time on March 14th, 1946. His complaints were those of recurrent epileptiform seizures of both petit mal and grand mal type since the age of 6. The boy was the product of a full term normal delivery, but he did not begin to speak clearly until 5 years of age.

The attacks became progressively worse after the age of 15 and there was very little response to dilantin and phenobarbital medication. After an attack, there was only partial amnesia for what had taken place.

During a typical minor attack, he recalled that there was a white light which made it impossible for him to see anything else. This was followed by turning of the head slowly to the right with the eyes turned up and somewhat

to the right, clonic movement of the head, and when the tongue was protruded on command during a seizure, there was a tendency to slow tremor. When something was held before his eyes during a seizure, he could not remember what it was, but he could remember things that were said for a certain period during the attack. Occasionally, with his major attacks there was raising of the right arm. The minor attacks came with extreme frequency.

Physical examination revealed no abnormality other than posterior flattening of the skull, and some slowness of mental response. The patient was predominantly left handed although he wrote with his right hand.

C.S.F. examination showed a negative Wassermann reaction and the proteins were within normal limits. Psychological tests revealed that the patient had fallen from a slightly above average value to one which was below average, although above the defective range of intellectual capacity. Pneumographic study revealed only a moderate generalized dilatation of the ventricular system.

Electroencephalographic examination by Dr. Jasper on March 25, 1946, showed that the attacks were associated with a bisynchronous discharge, maximum in frontal regions. There was paroxysmal wave and spike abnormality, and phase reversal study suggested the right anterior frontal region was nearest to the focal pacemaker.

The posterior flattening of the skull and the slowness in learning to speak suggested that there was some cerebral lesion which might be acting as a focal origin for the epileptiform discharge. On March 27, 1946, bilateral trepanations were made and intracranial electrodes were placed along the longitudinal fissure, under the orbital surfaces and upon the anterior frontal regions of right and left frontal lobes by Dr. Theodore Rasmussen. The electrocortigrams thus obtained seemed to indicate that the area of maximum potential discharge was from the right cingulate gyrus at the genu of the corpus callosum. Rapid transmission occurred from the right to left frontal poles.

The patient was discharged on April 6, 1946, on a trial of tridione and phenobarbital medication.

Second Admission

On April 15, 1946, the patient was admitted for the second time. The patient went into status epilepticus two or three times while in the hospital, which had to be controlled with paraldehyde.

At the suggestion of Dr.Jasper, on April 18, 1946, Dr. Penfield carried out a right frontal craniotomy and sectioned the corpus callosum in its anterior portion, in an attempt to abolish spread of the abnormal discharge from the right to the left side. Unfortunately this procedure did not abolish the spread from right to left, and upon

repeated electrographic examination, there was now an apparent maximum of discharge from the left frontal region.

He was discharged on May 8, 1946, on tridione and phenobarbital medication.

Third Admission

On September 4, 1946, G.K. was admitted for the third time. Following his last operation, the boy had had a marked decrease of clinical attacks up until August 15th. After this date, there was a marked increased in minor seizures, but he had had four major attacks since the operation.

Upon admission, the patient's condition was desperate; he was having minor attacks frequently as often as one every two minutes. After electrographic study on the day of admission, Dr. Jasper noted that, "it must be concluded that the origin of this discharge is in some centrally placed pacemaker possibly in the thalamus controlling the discharges in the left and right frontal lobe".

Because of the almost continual seizures uncontrolled by medication, and the electroencephalographic interpretation, the third ventricle was explored by Dr. Penfield on September 13, 1946, with the hope of determining an electrographic focus in this region.

A midline approach was made through the corpus callosum and fornix under local anaesthetic (nupercaine and adrenalin). During the entry into the third ventricle, the patient became deeply unconscious, and the patient ceased to have any seizures. The electrccortigrams showed a record which resembled deep sleep.

During the operative closure, the patient moved both his arms and legs. Within a few hours he again began having seizures. His plantar reflexes were flexor in response.

On September 15, the patient was given a repeated dose of nupercaine and adrenalin as at operation, in the leg, but there was no change in the frequency of his seizures.

On September 20, one week after operation, G.K. again was having repeated seizures of the same pattern as before operation. He was described at this time as rather apathetic and dull, but there were no abnormal neurological findings and rough aphasic tests showed no abnormality of speech.

On September 24, the third ventricle was explored for the second time by Dr. Penfield, and electrodes were placed on the frontal lobes and the cingulate gyrus as well as the walls of the third ventricle. Lateral traction was placed on the right thalamus directly behind the foramen of Monro and during the compression of this area the patient again became unconscious and hard to arouse; his seizures which

had been frequent up until that time again disappeared. During the procedure, there was a good deal of bleeding and injury to this region. No definite results were obtained on stimulating the left thalamus, but on stimulating the right thalamus (which had been injured) three per second slow waves were conducted to both frontal regions.

With the loss of consciousness, the respirations were 8 per minute; there was no response to painful stimulation but on pricking the soles of the feet there was withdrawal of the corresponding leg.

Postoperative Course

September 25:

There had been no spontaneous movement or speech since operation. The left hand grip was weaker than the right; there was a grasp reflex present on the right side, and the abdominal and cremasteric reflexes were absent on the left.

There had been no further seizures.

September 26:

There was no response to any form of stimulation. The plantar reflex was extensor on the left. Lumbar puncture showed pressure of 220 mm. of water.

In order to preclude the possibility of postoperative haemorrhage, a reopening of craniotomy and exploration was made by Dr. Penfield without anaesthesia. No clot was found

and there was no great increase in intracranial pressure.

September 27:

The patient was still unconscious, with no response. The eyes, however, were open and followed moving objects; the pupils were small and equal and reacted to light and accommodation. The plantar reflex was extensor on the left side.

September 30:

There was verbal response of a few words on repeated questioning. There was no weakness of arms, but the left leg showed slight weakness. There was forced grasping of right hand.

October 1:

The patient had been doubly incontinent since operation; on this day he had a typical seizure as noted before operation. Plantar reflexes were both flexor.

October 4:

The state of consciousness remained unchanged; he was apathetic and showed no initiative or spontaneous activity. There was a grasp reflex present on the right side.

October 10:

There was a central type left facial paresis, but the plantar reflexes were flexor and an ankle clonus was present on the left side. There was only occasional response of a few words to repeated questioning and there was no dysarthria.

October 12:

A ventricular needle was inserted into each anterior horn and produced some slightly blood stained fluid, but there was no increase of manometric pressure.

October 25:

Bilateral ventricular punctures were carried out; the pressure was 110 mm. of water in each manometer.

October 28:

The electrogram showed no epileptiform discharges throughout. The record was characterized by extremely slow random delta activity with occasional low voltage 6 per second disturbances and a few 14 to 16 per second spindles similar to those observed in normal sleep. This record was consistent with rather extreme generalized depression of cortical function, in some respects suggesting involvement of the sleep mechanism.

November 3:

Patient followed nurses with his eyes. He did not seem to have the slightest interest in his environment. He had to be tube-fed, and seemed to be in a constant state of impaired consciousness.

Withdrawal was elicited by stimulating the limbs, the legs being more active in response than the arms.

The temperature was normal; there had been no pilo-erection or flushing of the skin. The grasp reflex could not now be elicited.

November 10:

He had one seizure of the same type noted before operation.

December 7:

The course now took a severe turn for the worse; in spite of tube-feeding, he became markedly cachectic.

December 17:

With passive movement of the head the eyes moved in the opposite direction, but there was no change in posture of the limbs. There was no withdrawal reaction on painful stimulation of legs. No grasp reflex was present, and there was no suggestion of decerebrate rigidity.

December 19:

The electrogram was composed only of very slow delta waves (between about 1 and 5 per second) with no epileptiform discharges observed with the possible exception of some of the slow waves which had a sharp wave front.

It is remarkable that normal rhythms from the entire cortex were abolished and replaced by very low voltage slow waves, especially in parieto-occipital regions and in frontal regions, with the highest voltage of slow waves over the right temporal region.

The record was very similar to that obtained in extremely deep, normal sleep.

January 5, 1947:

Cachexia became more marked in spite of intragastric feeding and the patient died apparently of cachexia on this date, three and one half months after operation.

Summary of Postoperative Course:

Dr. Steelman summarised the postoperative condition of this patient as follows:

" The state of consciousness varied from drowsiness to actual stupor. This developed during the first forty-eight hours of the postoperative period. There was no spontaneous speech. At times, he would respond to questions using only several words for an answer, while at other times no response could be elicited. There did not seem to be any difficulty in articulation of the words which he spoke. He would chew and swallow food if placed in his mouth, but would not make any effort towards eating on his own initiative. In fact, he would show no interest whatsoever in food placed before him. For days on end, he would lie in the same position if not moved; actually, of course, his position was changed every two hours. He never at any time showed any initiative to do anything whatsoever that would indicate that he had any interest in his environment. For the first seven to ten days postoperatively, there was slight weakness of the left arm and leg and an extensor Babinsky response was

elicited for some weeks after operation.

"The state of consciousness became more stuporous and finally he would not respond to any sort of stimulation. At this time it was necessary to administer intragastric feeding.

"It should be noted that he would sleep if not bothered."

Necropsy:

Apart from emaciation and passive hyperaemia of the lungs, there were no significant abnormalities in the general autopsy examination.

On examination of the cranium, the skin and bone flaps were well united. The dural flaps below them were well healed and showed no blood clots.

Gross

There was no abnormality of the spinal cord or cortex. The brain was studied by means of coronal sections. In the right diencephalon a large cyst was found which extended from the level of the optic chiasm to the posterior commissure. It was larger in the anterior portion where it measured 4 cm. in diameter and the cyst tapered off gradually in size posteriorly. It was lined by a thin yellowish-brown fibrous membrane. In its anterior half, it was continuous with the third ventricle. (See Figs. 4 and 5.)

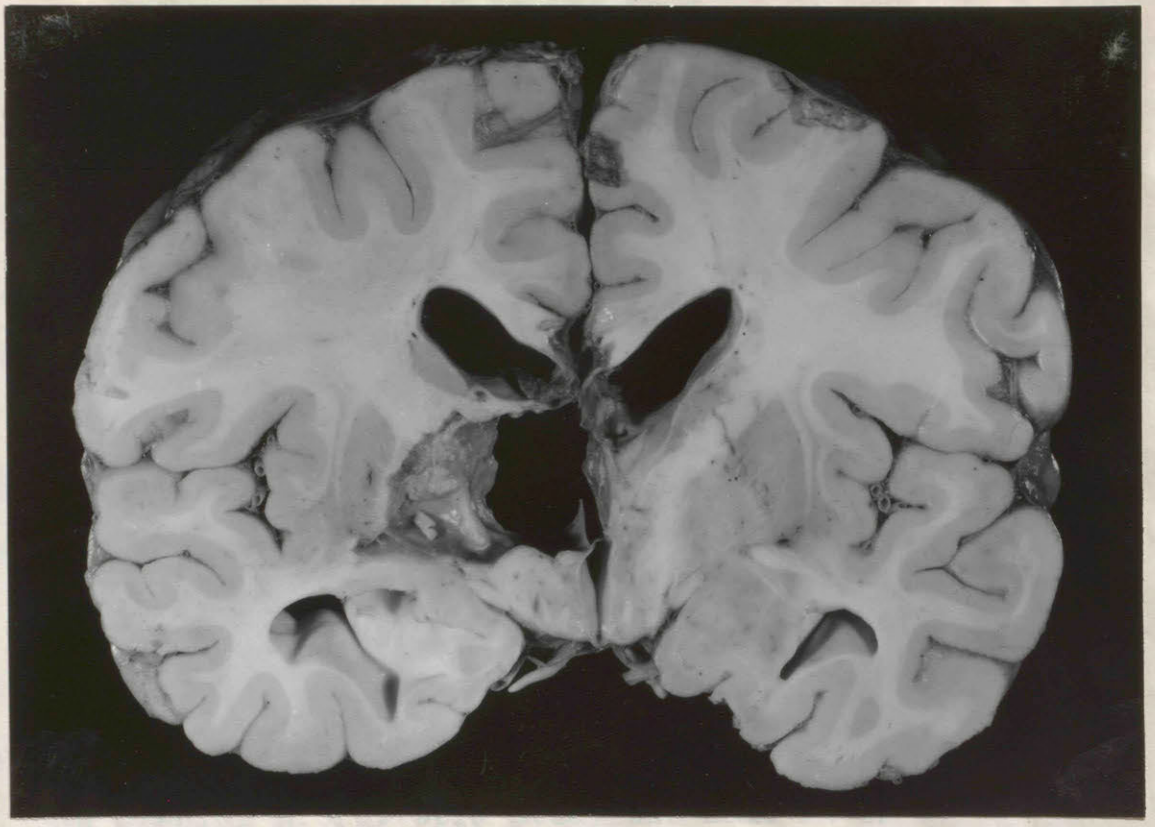


Fig. 4

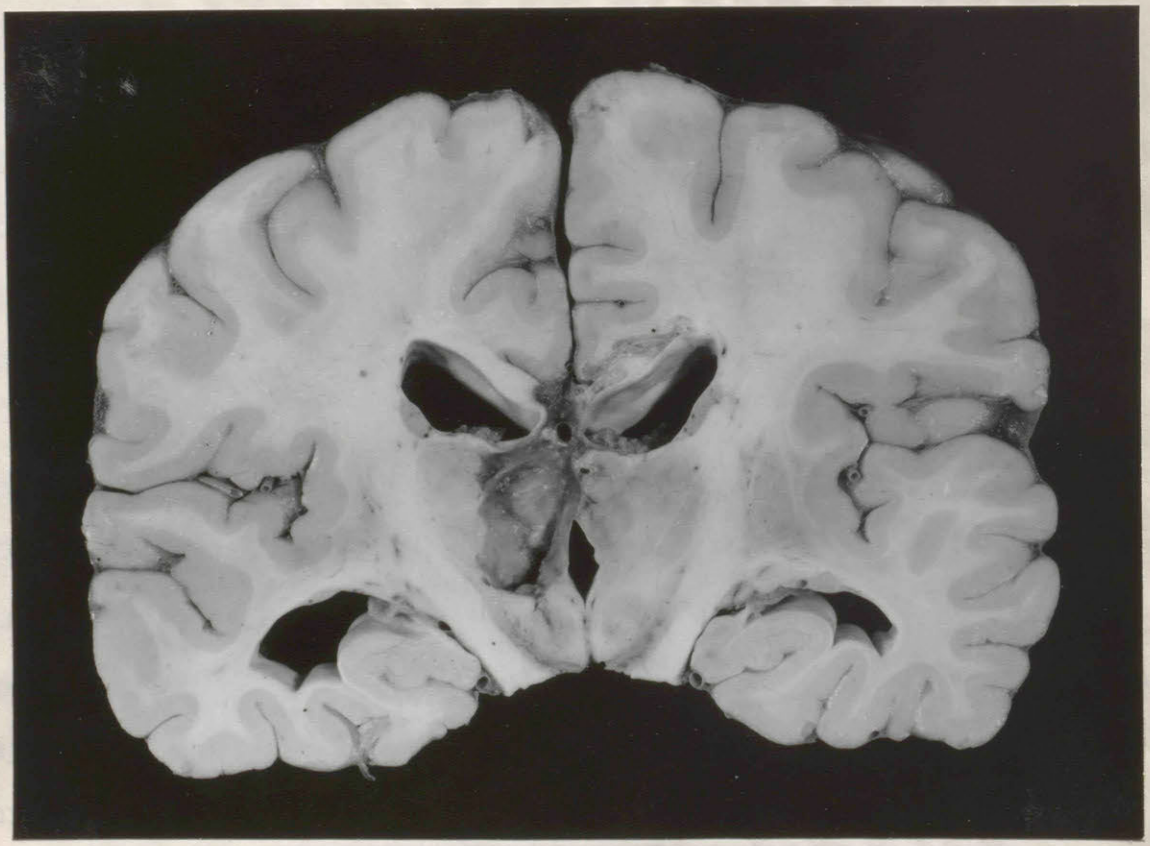


Fig. 5

Case G.K. Coronal sections showing the site of the lesion in the right diencephalon.

The right globus pallidus and the right thalamus were mostly replaced by this cyst. The red nucleus on the right side was involved slightly at its superior margin.

The mid-portion of the roof of the corpus callosum contained an operative defect which had been repaired with fibrous tissue.

The pia over the right frontal lobe was thickened and yellow.

Microscopic

A special microscopic study was made in order to correlate thoroughly the pathological findings with the clinical course of the patient. The coronal sections were cut into blocks which included the entire diencephalon and were embedded in celloidin. Serial sections were then cut at 50 mu and every fourth and fifth sections were retained. The sections were alternately stained with iron hematoxylin for myelin, and aniline-thionine for cytological study.

Anteriorly the lesion began as a cyst in the right globus pallidus at the level of the anterior commissure and the optic chiasm. There was some very slight extension into the anterior limb of the internal capsule but the degree of myelin degeneration was very slight. The genu of the internal capsule was intact. More posteriorly, the lesion extended medially through the inferior portion of the anterior limb of the internal capsule and the inferior limit of the head of the caudate nucleus to communicate with the third ventricle. The

corpus callosum had been passed in the midline just below the longitudinal fissure and the fornix had been destroyed. The defect in the corpus callosum had been healed by very vascular connective tissue. This defect in the corpus callosum and the destruction of the fornix were found in all sections studied. The only remaining recognisable portion of the fornix was the anterior columns on both sides as they descended at the level of the anterior commissure. They showed some myelin degeneration. The septum pellucidum was intact. More posteriorly, the cystic lesion became larger and its membranes well defined. In the Nissl preparations this membrane appeared to consist of a mesodermal glial reaction with a rich admixture of hemachromatin filled compound granular corpuscles. The blood vessels in the neighbourhood of the lesion were surrounded by these glial macrophages and many of the blood vessels were filled with these cells. At the posterior limit of the optic chiasm the lesion had destroyed most of the right globus pallidus. The lesion was far removed from the hypothalamic nuclei and the cells of the hypothalamus showed no abnormal change. All of the hypothalamic nuclei here identified were intact.

In sections behind the crossing of the anterior commissure and the optic chiasm, the lesion had destroyed about ten percent of the head of the caudate nucleus in its posterior and inferior

portions. There was complete severance of about 1 cm. in extent of the inferior portion of the anterior limb of the internal capsule and the entire globus pallidus had been enucleated and there was some destruction of the putamen in its extreme inferior and anterior portion (about 5 per-cent of its substance was destroyed). Although there was some chromatolysis of the cells of the putamen on the right side, this was not marked. At the level of the anterior portion of the red nucleus and the substantia nigra, the cyst involved the anterior and medial portions of the thalamus. The lesion had deeply enucleated the anterior nuclei, the nuclei of the midline, the dorsomedial nucleus, the internal medullary lamina, the nucleus centrum medianum, the medial part of the lateral nucleus and the anterior part of the nucleus ventralis lateralis on the right side. On the left side there was haemorrhage and gliosis of the anterior nucleus and the superior group of the nuclei of the midline. Passing backwards the destruction of the right thalamus remained relatively constant although more posteriorly the nucleus lateralis and nucleus ventralis lateralis were involved to a slight degree; but the anterior thalamic nuclei, the dorsomedial nucleus and nucleus centrum medianum were destroyed throughout.

The pedunculi and subthalamic nuclei were intact on both sides but the substantia nigra showed degeneration in its superior and lateral one quarter where a silver clip had

been placed on the left side on one of the thalamo-perforating arteries. This artery supplies the anterior and medial portions of the thalamus.

At the level of the mammillary bodies, both mammillary bodies appeared intact. But on the right side the cyst had destroyed the mammillothalamic tract and this tract showed severe degeneration in the neighbourhood of the cyst. At this level most of the entire right thalamus had been enucleated. (See Figs. 6 and 7.)

At the level of the central point of the red nuclei, the cyst occupied the entire thalamus except for the major part of the lateral nuclear mass. There had been a small haemorrhage into the right red nucleus but this degeneration did not involve more than forty percent of the cells of the red nucleus. On the left side the nucleus anteromedialis and nucleus anterodorsalis were replaced by a region of haemorrhage and gliosis. The nucleus anteroventralis could not be recognised and had apparently been destroyed together with the superior nuclei of the midline. The rest of the left thalamus was intact, including the left dorsomedial nucleus.

The left thalamus showed no cytological change other than that in the anterior and superior midline nuclei which was of a recent nature. After careful examination, particularly in the region of the dorsomedial nucleus and the intralaminar nuclei, it was concluded that there was no change in the blood vessels and in the

Fig. 7

Case G.K. Myelin Stain (X3).

There is complete destruction of the right thalamus except for the lateral nuclear group. There is slight damage to the right red nucleus. The left thalamus shows damage to the anterior nuclei and nuclei of the midline.

glia. In the posterior limits of the lesion, the nuclei of the midline on the left side were not damaged and the lateral portion of the nucleus anteroventralis on the left side showed about thirty percent of its cells to be intact. On the right side the lesion extended as far back as the medial pulvinar nucleus. Although in its posterior part the cyst did not involve the right anterior nucleus, this nucleus showed severe gliosis and all cells had disappeared.

Summary of Microscopic Findings

The corpus callosum had been severed in the midline. The body of the fornix had been destroyed; the right globus pallidus had been destroyed; there was slight involvement of the right caudate nucleus, the right anterior limb of the internal capsule and a very small region of the right putamen. There was a small region of haemorrhage into the right red nucleus and slight involvement of the superio-lateral parts of the right substantia nigra. The pyramidal system was intact. The lesion was essentially, however, a cystic degeneration of the right thalamus which involved the entire anterior nucleus, dorsomedial nucleus, nuclei of the midline, intralaminar nuclei and the internal medullary lamina together with the anterior part of the lateral nuclear mass. On the left side there was complete destruction of the nucleus anterodorsalis and anteromedialis and of about 75 per cent of the nucleus anteroventralis. There was also some destruction of the superior and anterior nuclei of the

midline. (See Fig. 8.)

Comment. It was impossible to conclude whether there was a massa intermedia present in this case, but in one series of about five sections the arrangements of the ependyma entirely around the third ventricle below the nuclei of the midline suggested that a massa intermedia was present before the occurrence of the lesion.

Analysis of Case G.K.

Following the second operation, there were two developments of a remarkable nature:

1. Electroencephalographic changes with replacement of normal rhythms by very low voltage slow waves especially in parieto-occipital regions and in frontal regions.
2. Almost total cessation of speech, absence of spontaneous movement, and profound impairment of consciousness.

1. Electroencephalographic changes with replacement of normal rhythms by very low voltage slow waves especially in parieto-occipital regions and in frontal regions.

This remarkable replacement of normal cortical rhythm by slow delta waves (between about 1 and 5 per second and similar to deep sleep) have been described in lesions of the third ventricle (Walter, Griffiths and Nevin, 1939; Cairns, Oldfield, Pennybacker and Whitteridge, 1941; Cobb, 1945).

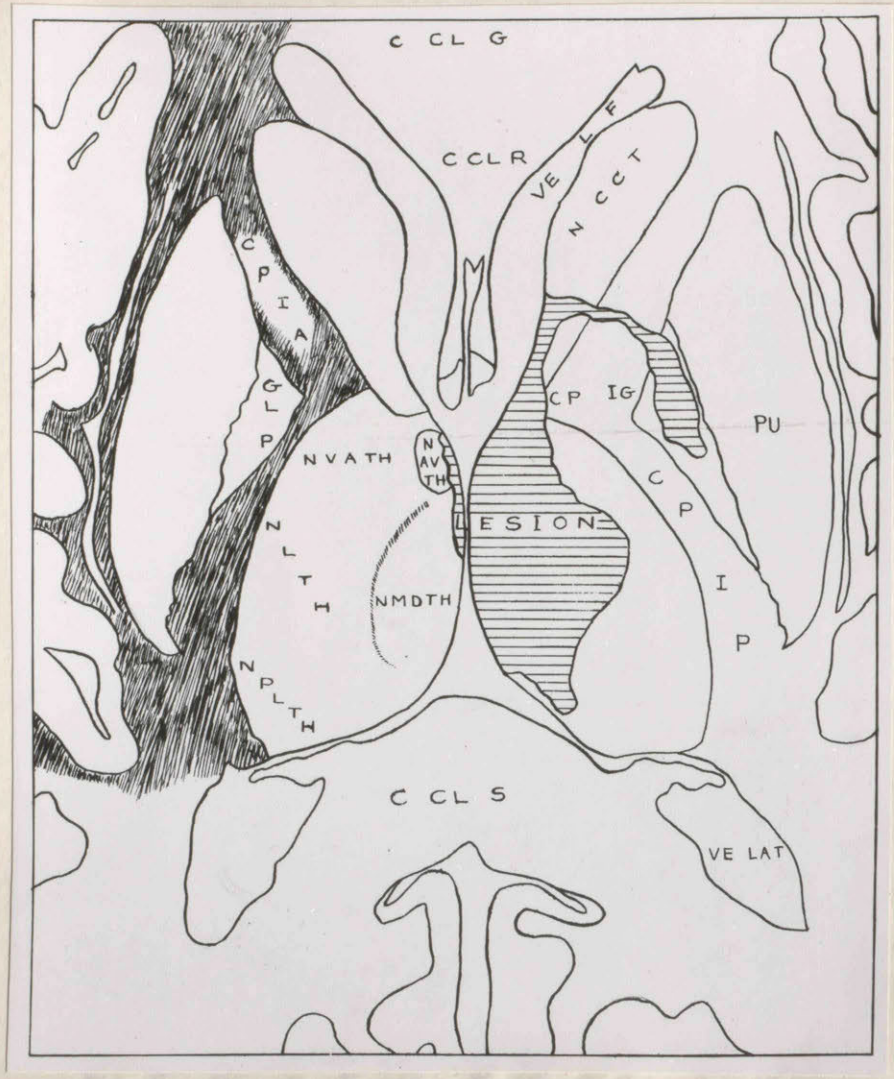


Fig. 8

Case G.K.

The site of the lesion at necropsy. The extent of the lesion has been superimposed on a horizontal section through the diencephalon at the level of the foramen of Monro.

C CL G	Corpus callosum, genu
C CL R	Corpus callosum rostrum
C CL S	Corpus callosum, splenium
CP I A	Capsula interna crus anterius
CP I G	Capsula interna genu
CP I P	Capsula interna crus posterius
GL P	Globus pallidus
N L TH	Nucleus lateralis thalami
N P L TH	Nucleus pulvinaris lateralis thalami
N V A TH	Nucleus ventralis anterior thalami
PU	Putamen
VE LAT	Ventriculus lateralis

After Riley (1943)

In the light of recent experimental work (Dempsey and Morison, 1943; Jasper and Fortuyn, 1947) demonstrating the influence of the anteromedial thalamus on the entire cortical rhythm in lower animals, it seems possible that these slow waves represent the cortical imprint of thalamic injury. The fact that stimulation of the injured right thalamus produced 3 per second slow waves conducted to both frontal regions would tend to support such a theoretical concept. It is further possible that the decrease in seizures, both electrographically and clinically, following both explorations was due to either temporary alteration of some "central pacemaker" initiating the abnormal rhythm, or to pathways essential for the conduction of the abnormal discharge.

2. Almost total cessation of speech, absence of spontaneous movement, and profound impairment of consciousness.

This complex was described by Cairns, Oldfield, Pennybacker and Whitteridge (1941), in their important case of third ventricle cyst, as "akinetic mutism". They postulate the syndrome to be due to a primary disturbance in the hypothalamico-thalamic pathways alongside the third ventricle although they could make no pathological study of the exact areas involved. However, they were able to demonstrate on three different occasions (by repeated drainage of the cyst) that this state was readily reversible and that the child had

complete amnesia for the period of akinetic mutism.

As in their case, we are able to rule out intracranial tension as a cause of this state, as ventricular puncture proved the pressure to be normal.

Since unilateral lesions of the sensory thalamus have a well defined symptomatology (Dejerin and Roussy, 1906) without akinesis, mutism, or impairment of consciousness, it seems logical that involvement of this area was not the primary factor.

Section of the corpus callosum was carried out on April 18, 1946, and following this procedure there was no alteration in consciousness, activity or speech; furthermore, agenesis of the corpus callosum is not an infrequent finding without such symptoms (Hyndman and Penfield, 1937).

Transection of the fornix can also be carried out without the development of these symptoms.

The unilateral destruction of the globus pallidus and slight damage to the putamen, caudate nucleus, red nucleus, and substantia nigra would not account for such a state in the light of most clinical and experimental studies (Wilson, 1940; Mettler, 1942; Davison, 1942). However, in a series of tumours of the third ventricle and retrograde thrombosis of the anterior cerebral artery one author concluded that the corpus striatum is essential to consciousness (Dandy, 1946).

The hypothalamus was not injured in this case.

For these reasons we may conclude that this curious state was caused by the destruction of the anterior nuclei and nuclei of the midline bilaterally, and the unilateral damage to the dorsomedial and intralaminar nuclei and adjacent fibre systems.

Summary of Case G.K.

A case of akinetic mutism and profound impairment of consciousness lasting three and one half months is described, in a right handed, young male, resulting from a lesion in the diencephalon. From the pathological study, it is concluded that the syndrome is produced by predominantly unilateral damage to the right anteromedial thalamus.

CASE E.K.

Ependymoblastoma of the diencephalon.

An 18 year old girl (E.K.) was admitted to the Montreal Neurological Institute on February 6, 1945, with complaints of headache, stiffness of the neck, spots before the eyes, difficulty with vision and diplopia. The first three symptoms were the earliest, beginning in September 1944; before this her health had been good. For the previous year she had tended to be a heavier sleeper, and had to be aroused. She was obese, but had lost 55 lbs. in weight during the previous year by dieting. The visual difficulty and diplopia began in November 1944,and in December 1944 these symptoms became more severe. In January 1945, she noted occasional tinnitus

in the left ear.

The family history was not contributory. The past history revealed that her birth was spontaneous, and her developmental progress normal. She had not suffered from diseases other than the common diseases of childhood, and there was no history of trauma or operation. Previous to admission she had not been confined to bed; she was left handed, and had taken thyroid extract for the previous six months.

Physical examination revealed an obese girl weighing 163 lbs. with no complaints at the actual time of examination. There were no abnormal findings in the chest. The blood pressure was 120/70, and the pulse was regular. The neurological examination did not demonstrate any rigidity of the neck. Mentally she appeared well oriented. There was papilloedema present bilaterally and lateral nystagmus. The hearing was slightly diminished on the left side, but the acuity was within normal limits. The abdominal reflexes were doubtfully elicited in all four quadrants. No other abnormalities were demonstrated by physical examination.

Investigation

On February 7, 1945, the Blood Wassermann was negative, and radiography of the skull revealed moderately prominent convolutional markings in the frontal bone, but no separation of the sutures. The left anterior clinoid was smaller than the right; there was no displacement of the pineal.

On February 9, opthalmological consultation was sought, and the fundi were described as having double choked disc, with 3D swelling of right and 4D swelling of left. The visual fields showed slight peripheral constriction.

On February 13, the C.S.F. Wassermann was negative. The ventriculogram showed good visualization of the left lateral ventricle which was dilated. A discretely outlined filling defect was present in portions 2 and 3. This filled a large portion of the ventricle but it did not obstruct its lateral part. The septum pellucidum was displaced to the left superiorly. There was practically no visualization of the right lateral ventricle. There was a rounded filling defect in the superior part of the third ventricle behind the foramen of Monro. The radiologist (Dr.W.E.Childe) expressed the opinion that, "There is a rather extensive intraventricular neoplasm best shown on the left side but presumably larger on the right side. The available evidence suggests that this also involves the superior portion of the third ventricle". (See Fig. 9.)

Operative Procedure

A left frontal osteoplastic craniotomy was performed on the same day. Dr. Penfield's operative report stated:

"There was a grayish-red, rather soft neoplasm just beneath the corpus callosum, and extending into the lateral ventricle on both sides. It seemed to have

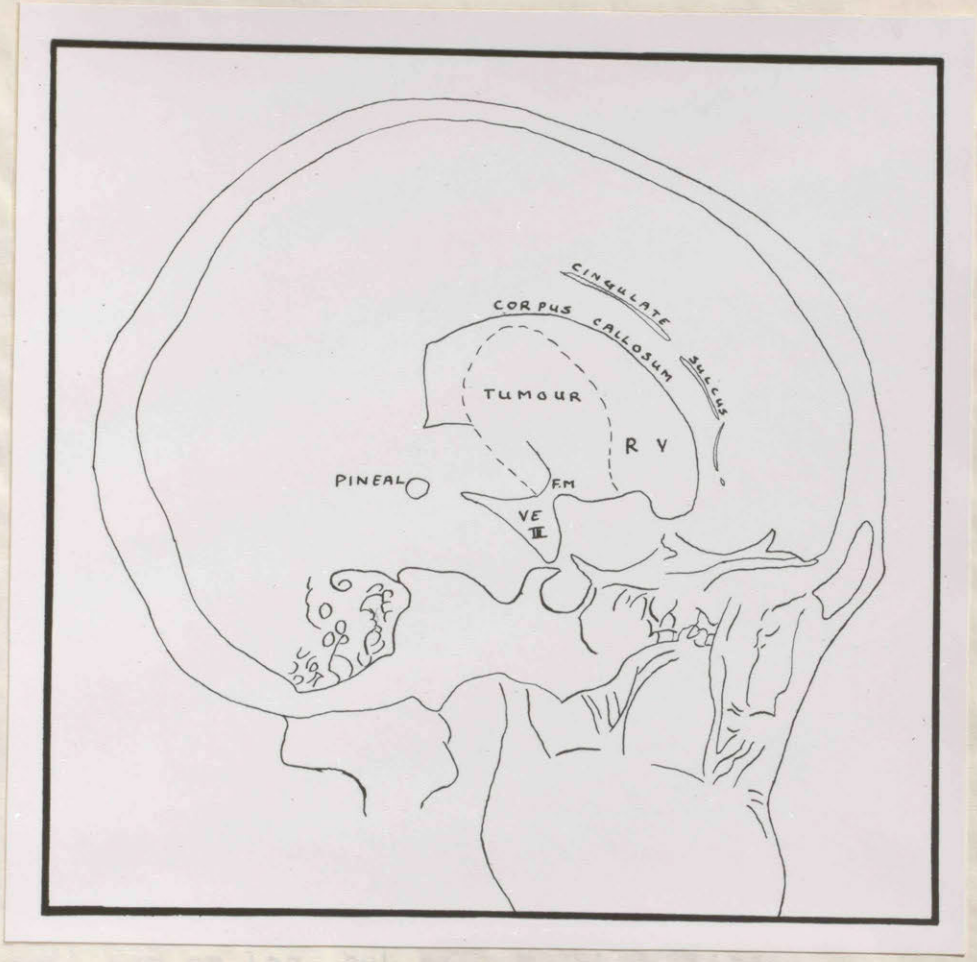


Fig. 9

Case E.K.

Ventriculogram tracing showing site of tumour in the lateral ventricles and superior portion of the third ventricle in the region of the foramina of Monro.

a fairly definite border.

"The frontal lobe was reflected from the mid-line; the corpus callosum was opened by suction and the neoplasm found immediately beneath.

"The neoplasm was removed from within itself for the most part. It extended well over the opposite side, beneath the edge of the falx, and the size of the tumour must have been about that of a plum. It was not particularly vascular.

"During the procedure, it was noted that the patient rather suddenly stopped talking. This occurred when the neoplasm was nearly removed. At first she would answer when urged, but then she answered no more. A little after that Miss Elliott noted that she did not seem to be using her right arm or leg, but was only using her left. At the close of operation, however, I found that painful stimulation of the right hand caused her to move it, but that she had a positive Babinsky in the right foot, and negative in the left. She made quick movements with her left hand as though trying to call attention to things, but would not respond to any commands. I asked her to squeeze my hand but there was no movement. At other times, however, she tapped on things as if trying to attract attention, and then might reach toward an area which was being hurt.

"Fibrin foam was used to stop oozing. The dura was closed, and when this was done, the circulation of the brain seemed to be quite satisfactory. There was no breaking of the cortex at any point. The retraction, however, may well have involved the motor area to some extent, particularly in the leg area. This would not, however, account for the stopping of speech.... The removal, after the neoplasm was out, was found to have carried down 7 cms. beneath the surface of the dura."

Surgical Pathology

Pathological study of the surgical specimen showed it to consist of pure neoplastic tissue, very uniform in type, and with no evidence of necrosis, and with occasional mitotic figures. There was a tendency for rosette formation suggesting that it was of the ependymoma or medullo-epithelioma group. It was classified as an ependymoblastoma.

Postoperative Course

Following the operation the patient did not respond in any way although slow withdrawal of the limbs could be elicited by painful stimulation. Her systolic blood pressure remained between 110 to 120 mm. of mercury for some ten hours postoperatively, when at 4 A.M. on February 14th her systolic blood pressure rose above 120 mm. for the first time.

At this time she began to have recurrent seizures, the components of which Dr. Penfield described as follows:

1. Hyperpnoea.
2. Retraction of neck.
3. Stiffening of legs in extension with plantar flexion.
4. Extension of arms, with acute flexion of wrists and thumb in palm and forearm supinated. (Occasionally left arm was not extended but flexed and drawn up to face with small delicate movements of fingers.)
5. Increase in pulse rate and decrease in volume, the pulse rate being 72 per minute between attacks, 120 per minute during attacks.
6. The body was dry and the extremities hot.

The eyes did not deviate during seizures; the pupils were equal, 2 mm. in diameter, and reacted to light. The attacks were opisthotonic with supination of hands. There was no evidence of vasomotor changes in the skin, and no sweating or lacrimation. The frequency of attacks was one every ten minutes, increasing to one every 1 to 2 minutes when stimulated.

The craniotomy wound was reopened on February 14th and a blood clot removed from the tumour bed.

The attacks continued at intervals of a few minutes despite this procedure, but on February 15, the attacks

became less frequent. The patient did not seem aware of her environment and did not speak. The plantar reflexes were both extensor. On repeated painful stimulation there was occasionally vocalization in the form of a low moan, but no words were uttered and there was no movement of the limbs. She was doubly incontinent and would only take fluids from the nurse who fed her and she had to be turned every hour. Her eyes, however, were frequently open and appeared to follow movements.

On February 16, an electroencephalogram was carried out by Dr. Jasper who reported as follows:

> "The electrograms from all head regions examined varied between continuous slow wave activity of moderate amplitude, at frequencies between 1 and 2 per second, to a record where there was very little of this slow wave activity and some alpha rhythm at about 6 to 8 per second of low amplitude.
>
> "The slow waves were present when the patient was having an opisthotonic seizure and at other times, when the patient was relaxed in complete quiet, the slow waves would disappear for short intervals and the low amplitude slow alpha would be present. Stimulation of any kind, either the sharp click of a telephone receiver, pin prick, or calling the patient's name, would serve to initiate the slow wave activity and often produce an opisthotonic attack.

"It is notable that the relation between the slow waves and stimulation is just reversed in this case from the normal effect on the slow waves of sleep.

"There was no evidence of the usual form of cortical epileptiform discharge during the opisthotonic seizures, there being only some muscle potential artifact superimposed upon the slow wave activity.

"Impression: It appears from the electrogram that the seizures of this patient are not associated with the usual cortical epileptiform discharge, but are associated rather with the inhibition of cortical activity as shown by large continuous slow waves from all head regions examined. Interpretation of the relation between slow waves and stimulation is not clear".

This state continued until February 20 when she began to improve and would squeeze hands on command but she did not respond verbally. There were no further opisthotonic attacks after February 26. Gradually, her expression appeared more alert and she responded more readily to commands although to a very limited extent. She spoke for the first time on the evening of February 26.

On February 28, when shown a pencil and asked if it were a hippopotamus, she laughed. Her speech gradually improved and at this time she spoke short sentences which were uttered with great hesitancy and with a tendency to

perseveration.

Progress continued steadily and uneventfully and the patient was discharged with no disability except weakness of the left leg on March 16, 1945. At this time she appeared well orientated, spoke easily and directly in answer to simple questions.

She returned home and seemed to be well until April 9, 1945, when she became very drowsy and was difficult to arouse. She was perspiring profusely and her temperature rose to 100. She became unconscious and her temperature had risen to 107 when she died on April 11, 1945.

Summary of Postoperative Course

Following the first operation the patient ceased to speak and to respond, and there were frequent opisthotonic and autonomic seizures. For this reason reoperation was carried out the following morning and a small clot was evacuated from the tumour bed. During the next week, the patient continued to have these attacks and was completely unresponsive, but on the 7th day following operation, she would take fluids by mouth and would squeeze both hands on command. Two weeks following operation there were no further opisthotonic attacks and she seemed more aware of her environment but she would not talk. Halting speech began within the next few days and her general improvement was slow but gradual.

At the time of her discharge on March 16, she was walking well but there was slight paresis of the left leg. Her speech at the time of discharge was fairly normal except for an apparent lack of emotional tone.

On April 9, she again became unconscious and died on April 11.

Anatomical Site of the Tumour

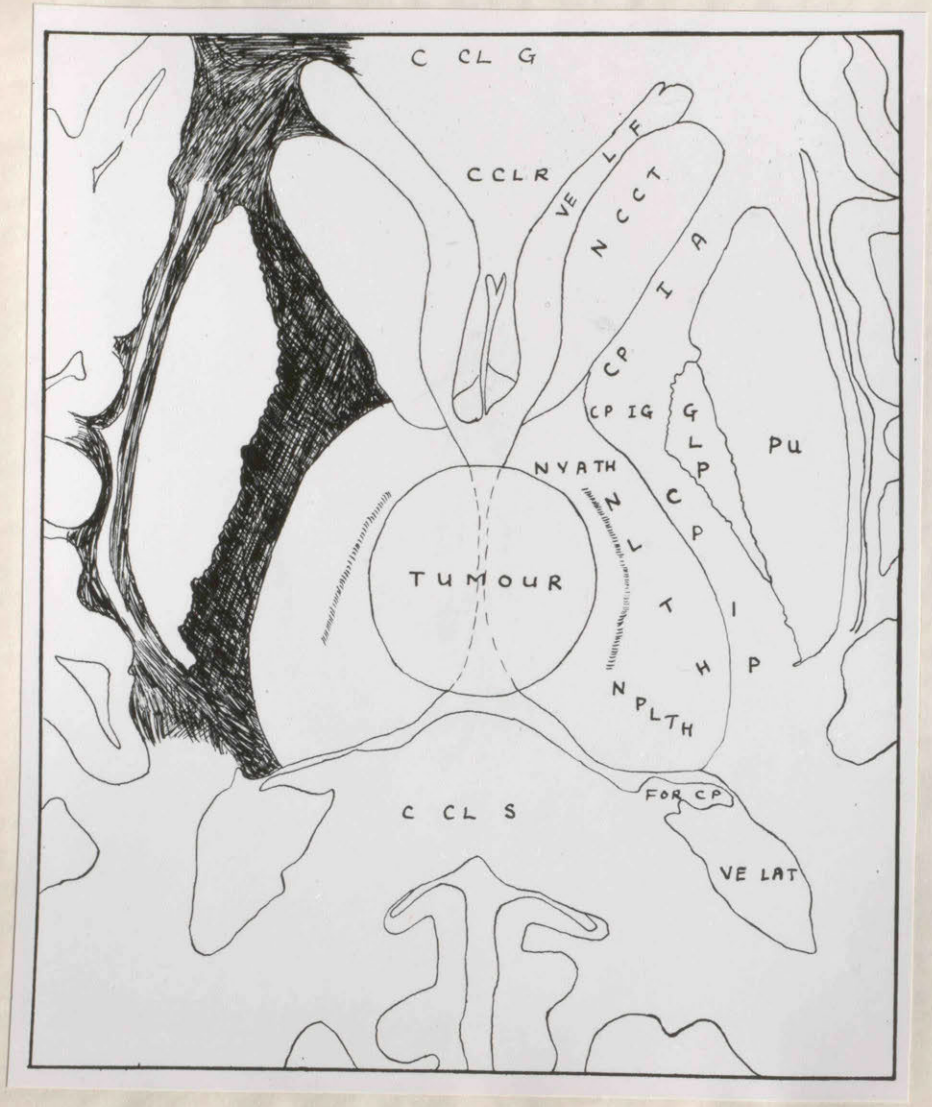
An autopsy was not obtained, but the site of the tumour was reconstructed from the ventriculogram and diagrams made at operation. The tumour lay between as well as above the anteromedial portion of both thalami. Since it lay behind the foramen of Monro, the tumour would be in relation to the dorsomedial nucleus and the posterior portion of the anterior nucleus of the thalamus on both sides. Infiltration of brain tissue is an extremely common feature of this type of glioma. (See Figs. 10 and 11.)

Analysis of Case E.K.

Following the removal of this tumour lying in a most vulnerable and inaccessible portion of the brain, there were two developments of a remarkable nature:

1. Temporary but total loss of spontaneous movement and speech with impairment of consciousness.
2. Electroencephalographic changes consisting of inhibition of cortical activity.

Fig. 10



Case E.K.

The site of the tumour as estimated at operation. The tumour has been superimposed on a horizontal section through the diencephalon at the level of the foramina of Monro.

C CL G	Corpus callosum, genu
C CL R	Corpus callosum, rostrum
C CL S	Corpus callosum, splenium
CP I A	Capsula interna crus anterius
CP I G	Capsula interna, genu
CP I P	Capsula interna crus posterius
FOR C P	Fornix, crus posterius
GL P	Globus pallidus
N L TH	Nucleus lateralis thalami
N V A TH	Nucleus ventralis anterior thalami
PU	Putamen
VE LAT	Ventriculus lateralis.

After Riley (1943)

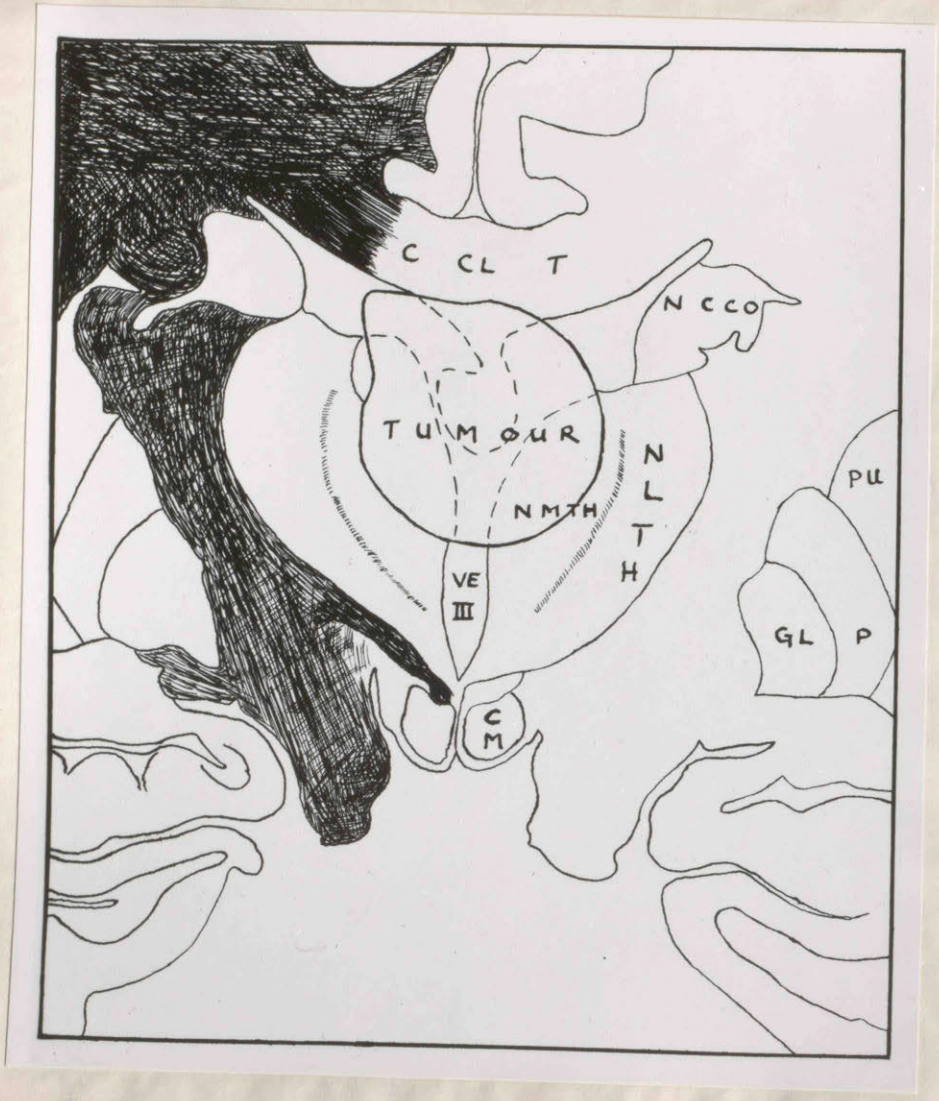


Fig. 11

Case E.K.

The site of the tumour as estimated at operation. The tumour has been superimposed over a coronal section through the diencephalon at the level of the foramina of Monro

C CL T	Corpus callosum, truncus
C M	Corpus mammillare
GL P	Globus pallidus
N C CO	Nucleus caudatus, corpus
N L TH	Nucleus lateralis thalami
N M TH	Nucleus medialis thalami
PU	Putamen
VE III	Ventriculus tertius

After Riley (1943)

1. Temporary but total loss of spontaneous movement and speech, with impairment of consciousness.

We have seen a similar syndrome of akinetic mutism and impaired consciousness in the previous case (G.K.) and concluded that this state may be produced by damage to the anteromedial thalamus. This remarkable change occurred in this case when the neoplasm was nearly removed and cannot be related to the approach through the corpus callosum, but must have been brought about during the necessary manipulation in the region of the medial walls of the thalamus. The fact that the change was only temporary in nature suggests that oedema in this region was responsible for the thalamic paralysis.

Damage to cortical areas which are related to the alteration and arrest of speech were far removed from the operative field, e.g., Broca's area, the angular gyrus, and the first temporal convolution. Similarly the area of vocalization in the face zone of the precentral gyrus could not have been involved.

The available evidence in this case would seem to substantiate the conclusion that akinetic mutism and impaired consciousness may arise following damage to the anteromedial thalamus.

2. Electroencephalographic changes

We have already suggested that such slow wave activity

might represent the cortical imprint of thalamic injury. In the case of G.K., direct electrical stimulation of the injured thalamic area produced cortical slow wave activity. In this instance, epileptiform activity,which the available evidence suggests was thalamic in origin,also produced similar cortical slow wave activity.

Summary of Case E.K.

A case is described where temporary but total loss of spontaneous movement, speech and impaired consciousness occurred following the removal of a tumour in the third ventricle. It is concluded that the akinetic mutism was due to damage in the region of the anteromedial thalamus.

CASE J.T.

Haemorrhagic cyst of the septum pellucidum.

Sister J.T., a 33 year old nun, was referred to Dr.Penfield's service on April 10, 1948, by Dr.R.Beaudry of Magog, Quebec. The patient had been well up until two months prior to admission, when she developed headaches of gradual onset. These headaches increased in frequency and severity, but were not associated with any visual disturbances.

On March 30, on assuming a standing position after stooping, the patient complained of severe headache. Then she stated she was hungry, but on being given a banana she did not eat it, but walked a few steps, fell on the floor

and vomited. On being picked up by the sisters, it was noticed that her body was stiff, particularly in the neck. Twenty minutes later she was brought to the nursing home under the care of Dr. Beaudry.

A sister who accompanied the patient when she was admitted to the Montreal Neurological Institute stated that she had spoken since the episode up until April 7, when there was cessation of speech. She had recognised her brother at times only, but she had followed the therapeutic procedures in the nursing home with her eyes. Her appetite had been excellent until three days before admission when she would only take gruel, and on the day of admission she would only take fluids.

Dr. Beaudry had instituted daily lumbar punctures until April 7, and the cerebrospinal fluid was repeatedly blood-tinged. The manometric pressure was recorded as 135 mm. of water on the last examination before admission.

Her temperature had ranged from 101° to 104° F. and she had been doubly incontinent since March 30.

There was no family history of hypertension or nephritis but her mother had become paralysed before she died at the age of 36.

Her birth and development during infancy were normal. She had entered school at 6 and continued until the age of 14. She had joined her religious order at the age of 17.

Her sister stated that she had had high blood pressure,

but otherwise she had always been healthy.

Menses began at 13 and her last menstrual period before admission was April 1, 1948.

Sister J.T. was right handed.

On admission examination, her blood pressure was 125/70, pulse 120, respirations 28, and temperature 104°F. The respirations were regular. The patient was well developed and nourished; the skin was of normal colour and the hair was of normal distribution.

The patient lay in bed with her eyes open, following the activities of the examiner. Pricking of the face or attempts at bending the neck produced a grimace on either side of the face. Painful stimulation, however, below this level produced no expression of pain. There were occasional movements of the mouth and tongue such as a sleeping individual may make, and she was seen to close her eyes normally. But she did not move her neck or any other part of her body and she did not speak.

Cranial nerves:

1. Unable to test.
2. Visual acuity apparently normal if synchronous movements of the eyes following moving objects may be taken as a valid indication of vision. The right fundus did not appear abnormal and the boundary of the optic disc was well defined. There was no haemorrhage or exudation. The left fundus,

however, showed a patch of haemorrhage just above the optic disc. The retinal veins did not appear engorged.

3,4,6. The pupils were round, the right being 4 mm., the left 3 mm. in diameter. They constricted to light and dilated in the dark. There was no nystagmus or strabismus.

5. The corneal reflexes were present.

7. The face appeared symmetrical.

8. There was no response to loud sounds.

9, 10. The pharyngeal reflexes were present and she swallowed well.

11, 12. Unable to test.

There was some extensor rigidity on admission. There was no movement of the extremities whatever. The reflexes both superficial and deep were normal except that no plantar response could be elicited.

There were grimaces on pinprick of the face, but below the chin, pinprick brought no response.

On April 11, the examiner (W.P.) noted that now there was no increased tone, but there was rigidity of the neck on attempted flexion. The respirations had become Cheyne-Stokes. The blood pressure was 130/70 but the pulse pressure seemed small to palpation. The pulse was fast, between 100 to 130 per minute. Her temperature was 103, but her hands and feet were not cold, and her skin was dry. There was no shivering

but there was recurrent pilo-erection on the arms and legs bilaterally, and synchronous with the pilo-erection the nipples became puckered to a height of 1.3 cm.

The examiner concluded that there were two possibilities, first that of compression of the brain stem just below the nuclei of cranial nerves 9 and 10, with varying compression of the midbrain (to account for the varying rigidity). Against this first conclusion was the rapid pulse, and absence of pyramidal signs. The second conclusion was that there might be a lesion of the third ventricle and thalamus.

Because of the likelihood of compression of the mid-brain, a suboccipital decompression under local anaesthesia was carried out by Dr. Penfield on April 11, 1948. The following is a summary of the operative procedure.

"Bilateral burr holes for ventricular puncture were made and a needle put in the left lateral ventricle. The foramen magnum was approached through the occipital bone, the arch of the atlas removed and the dura opened. There was no increase of pressure in the posterior fossa, possibly because of the puncture of the left lateral ventricle. There was no evidence of subarachnoid haemorrhage.

"An attempt was made to estimate whether or not the third ventricle was obstructed. From the right ventricle, it was quite clear that fluid ran down and out from the posterior fossa, but this procedure could not be carried

out via the left ventricle, indicating a block of the left foramen of Monro.

"The lateral ventricles were large. The tonsil of the cerebellum appeared normal enough, but it extended down ½ cm. below the atlas.

"At the close of the operation, the Cheyne Stokes respirations disappeared and her breathing became rapid. There was withdrawal of the legs on painful stimulation. The plantar reflexes were flexor in response."

Three hours after operation the patient lay in a motionless state with the eyes open and following moving objects. The pupils were equal and reacted to light. There were no abnormal reflexes. The respirations were regular but varied at 36 per minute. The pulse was regular at 120 per minute and the blood pressure was 130/80. There was no response to repeated questioning and commands, and she did not speak.

On April 12, when examined, she lay in her typical mute and motionless state with her eyes open and following the examiner's face. Her expression showed no evidence of interest in her environment, but appeared totally apathetic. She had to be turned every two hours like a comatose or paralysed patient.

The respirations were 32 per minute, the blood pressure 130/64, the pulse 120 per minute, the temperature 103° F. The skin was warm and there was occasional pilo-erection and erection

of the nipples. The limbs were extended and motionless except for 30° of flexion at the elbows. The thumb was held between the ring and second finger, and the wrist held in the normal position of rest.

The right pupil measured 4 mm. and the left 3 mm.; both reacted to light.

A ventriculogram was carried out on April 12, and the following report was made by Dr. D.G. Wollin.

"There is no measurable shift of the septum pellucidum from side to side. The septum is grossly thickened however, especially anteriorly. The corpus callosum is also thickened anteriorly and the anterior horns of the lateral ventricles are separated. The medial walls of portions 1 and 2 are convex instead of concave or straight. The lesion seems to involve the floor of portions 1 on both sides. The foramen of Monro is displaced posteriorly and the anterior part of the 3rd ventricle also seems to be slightly displaced posteriorly. The entire septum pellucidum is involved. In the A.P. views, the outline of the septum pellucidum is elliptical and quite symmetrical on the two sides. Dr. McRae suggests that this indicates a haemorrhage in the septum pellucidum. It may also indicate a cyst. There is a cutout in portions 1 and 2 of the left ventricle. This is due to a deformity of the corpus callosum. The floor of portion 3 on the left side

is elevated slightly. The 3rd ventricle, except for the posterior displacement of its anterior recesses, is not deformed. The posterior portion appears quite normal. It is moderately dilated. The aqueduct and 4th ventricle are not visualized."

On the same day, April 12, Dr. Jasper reported the electroencephalogram as follows:

"This electrogram was severely abnormal from all head regions examined with no trace of normal cortical rhythms throughout the entire record.

"The record obtained was characterised by periods during which there were slow waves of frequency between 1.5 and 2 per second.

"The most interesting feature of this record was the variability from time to time. The brain waves practically completely disappeared at intervals with return of slow waves. Sometimes this flattening of the record would appear first on one hemisphere and then first on the other to progress to involve all scalp surfaces examined, causing generalised depression in voltage.

"Localisation studies failed to reveal any clear constant area of maximum abnormality at the head surface and there was no localisation made out at the base. Abnormal discharges were not bilaterally synchronous."

On April 13, a left frontal osteoplastic craniotomy was performed by Dr. Penfield, who made the following operative note:

Procedure:

A small bone-flap was turned far forward. The dura was opened, the ventricle punctured and the corpus callosum was cut. The left frontal lobe was retracted, and an opening made in the septum pellucidum. The anterior end of the corpus callosum was then removed and beneath it, the blood cyst was encountered.

Objective findings:

The brain was under greatly increased pressure until the left ventricle was punctured. The corpus callosum appeared rather glary and slightly puffed. Beneath the anterior end of the corpus callosum and extending downward and backward in a position just anterior to the third ventricle was a blood clot made up of old, black blood which could be several weeks old. The haemorrhage seemed to be within a cyst, but the cyst wall was very thin and yellowish in colour. The septum pellucidum behind the cyst was dark. An opening was made through the septum pellucidum from one lateral ventricle to the other.

Summary:

This patient had had a haemorrhage just anterior to

the third ventricle. Whether the haemorrhage was secondary to a neoplasm will have to be settled by microscopical studies.

At the close of operation, the patient withdrew her arms with painful stimulation.

Site of the Cyst

A drawing of the site of the cyst was made by the operator following operation. The cyst was in the midline, being about 2.5 cms. in diameter; it was 6 cms. below the scalp surface and pressing backwards on the anterior portion of the third ventricle. The foramen of Monro was closed by pressure on the left side. (See Figs. 12 and 13.)

Surgical Pathology

Biopsy specimens of the corpus callosum and septum pellucidum bordering the cyst were examined microscopically:

"From the tissue examined, there is no evidence of neoplasm. The findings are those of necrobiosis and replacement gliosis. Consideration of the operative findings and the pathological sections would seem to indicate that the process of gliosis is in response to the previous haemorrhage."

Postoperative Course

The patient showed little improvement during her postoperative stay in hospital.

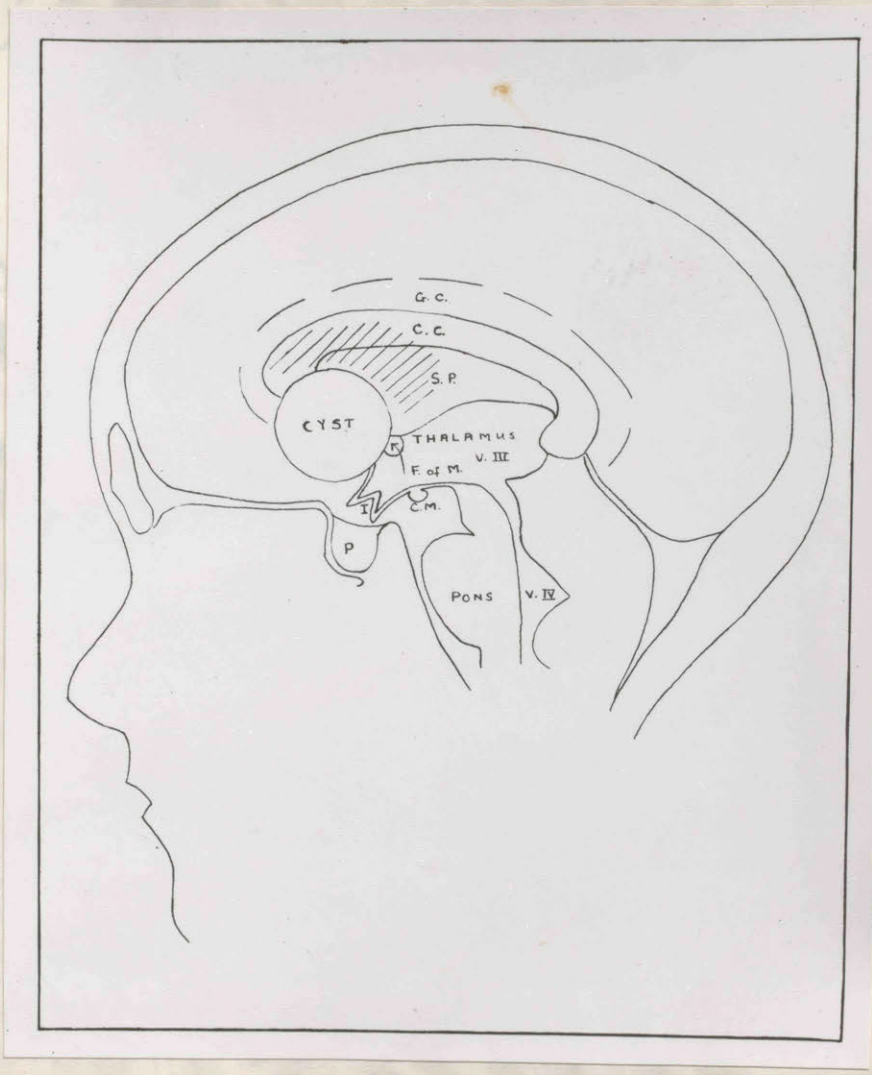


Fig. 12

Case J.T.

Diagram drawn at operation of the anatomical relations of the cyst.

G.C.	Gyrus cingulus	C.M.	Mammillary body
C.C.	Corpus callosum	P.	Pituitary
S.P.	Septum pellucidum	V.III	Third ventricle
F.of M.	Foramen of Monro	V. IV	Fourth ventricle

The shaded area represents the area of haemorrhagic infiltration around the cyst.

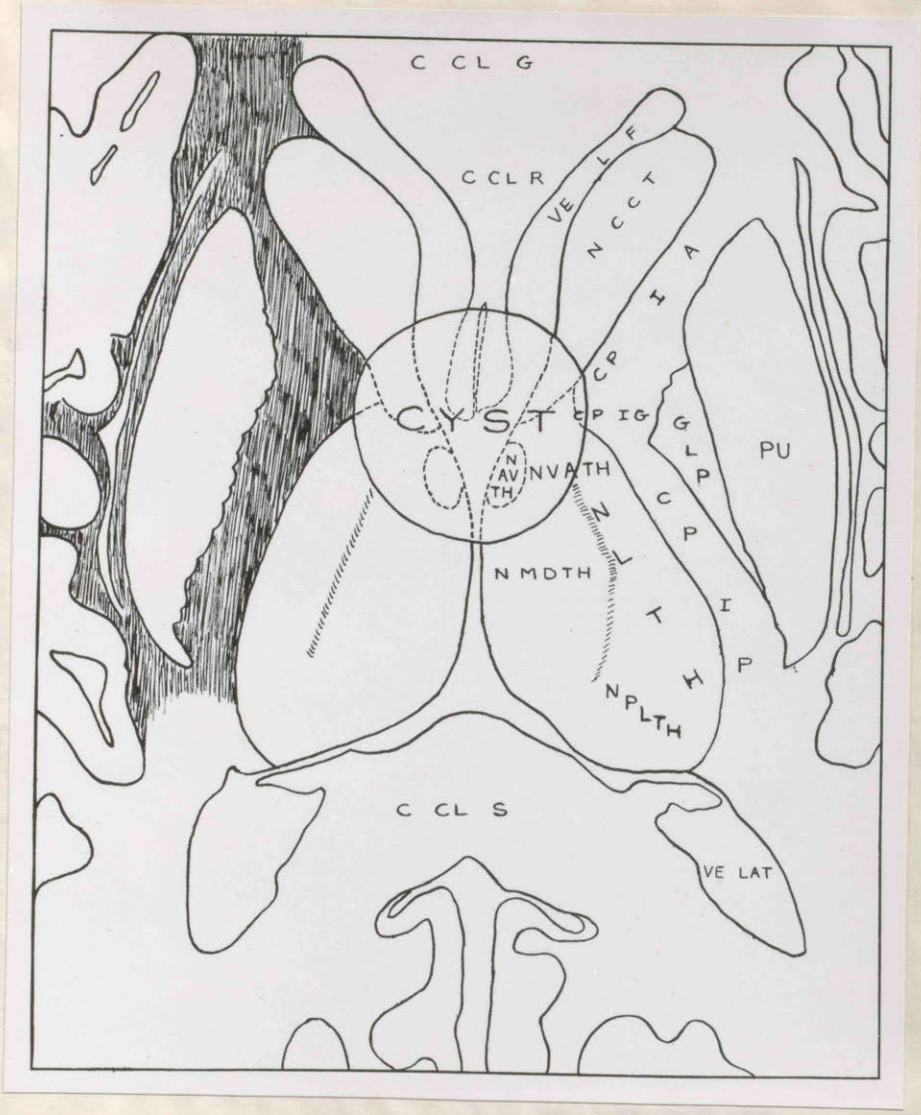


Fig. 13

Case J.T.

The site of the cyst as estimated at operation. The cyst has been superimposed on a horizontal section through the diencephalon at the level of the foramina of Monro.

C CL G	Corpus callosum, genu
C CL R	Corpus callosum, rostrum
C CL S	Corpus callosum, splenium
CP I A	Capsula interna crus posterius
GL P	Globus pallidus
N L TH	Nucleus lateralis thalami
N PL TH	Nucleus pulvinaris lateralis thalami
N V A TH	Nucleus ventralis anterior thalami
PU	Putamen
VE LAT	Ventriculus lateralis

April 14:

The pulse was 104 per minute, the temperature 100° F., and the respirations 22 per minute. The patient lay with her eyes open, but there was no spontaneous movement or speech. There were no abnormal reflexes. There was a facial paresis of the central type on the right side. The pupils were equal and reacted to light.

April 17:

Her strange state of absence of spontaneous movement remained unchanged; there was now an extensor plantar reflex on the left side. Recurrent pilo-erection was still present.

April 21:

Pulse 85, respirations 18 per minute. The corneal reflexes were present. There was a well-sustained grasp reflex of the left hand with no groping component. Her eyes followed movements and pin prick of the face produced a grimace. The facial paresis on the right side was now marked.

There was no response to questioning or commands, no spontaneous movement or speech. The plantar reflex was extensor on the left side.

She still had to be fed, but she continued to swallow liquids well.

April 24:

When first examined she had her eyes closed, but on raising her arm she opened her eyes and as usual seemed to follow activities in the nursing room. The respirations and pulse were regular and of normal rate. The grasp reflex was still present on the left side. There was no response to auditory or painful stimulation except grimace of the left face when the face was pricked. The reflexes were not abnormal, the plantar reflexes now both being flexor.

Her state of unconsciousness remained quite unchanged. She was discharged on this date to return to the nursing care of the sisters of her religious order.

The head nurse of the mother house, Soeur Marguerite de l'Eucharistie, made the following excellent summary of her progress up until September 20, 1948.

"Sister J.T. has been losing weight gradually although her general condition seems a little better. Her appetite is fairly good although at times she vomits, as many as three or four times a week, even though she has not eaten more than usual. Her blood pressure is 140/90 and her temperature between 99 and 100.

"In early July, Sister had convulsions three or four times a week. She seemed very low and we thought it best that she receive the last sacraments.

"You asked us if Sister can speak. She has never uttered a word although at times it seems as though she

tried to. Neither does Sister move by herself, but she is turned around every two hours, as usual. She moves her left arm and left leg but we do not know if it is voluntary. If there is someone in her room,or when she seems more tired,she will turn her head from right to left throwing it backwards, with eyes raised, like in a case of meningitis. She is still unable to eat by herself,but for the past week, when given bread or cookies she will take this food and bite it with appetite.

"She seems to take interest in people who come in her room by following them with her eyes and more recently she smiles as though she recognises them. The smile is only on the left side of her face, the right side being paralysed as when she was at the hospital.

"Sister J.T. does seem very drowsy at times. She does not sleep very well but when she does her eyes are closed like those of a normal person.

"We are unable to know just how conscious she is of what is going on around her."

Summary of Postoperative Course

Although the operative procedures relieved the Cheyne-Stokes respirations, the hyperpyrexia, the abnormal pulse rate and the intracranial tension by circumventing the block of the left lateral ventricle, her state of impaired consciousness, absence of spontaneous movement and speech

persisted. She never at any time was known to speak during her hospital stay and made no attempt to eat on her own initiative. If food was placed in her mouth, she would swallow it. She maintained the same position after being turned every two hours. Usually withdrawal of the limbs could be elicited by painful stimulation. A Babinski sign was present for some days after operation on the left side and a left facial palsy became evident in the first week after operation.

The grasp reflex on the left side persisted until discharge; but the Babinski reflex was not present at discharge.

Analysis of Case J.T.

Following the formation of a haemorrhagic cyst pressing upon the region of the foramina of Monro this patient demonstrated two remarkable phenomena:

1. The periodic replacement of brain waves by slow waves of frequency between 1.5 and 2 per second.
2. Total cessation of speech, absence of spontaneous movement, and profound impairment of consciousness.

1. The periodic replacement of brain waves by slow waves of frequency between 1.5 and 2 per second.

We have found such generalised slow wave activity in the other cases of thalamic damage (E.K., G.K.) and have

already suggested the possibility that such activity may be the cortical imprint of thalamic injury.

2. Total cessation of speech, absence of spontaneous movement, and profound impairment of consciousness.

We have encountered this state of impaired consciousness and akinetic mutism in two other cases (E.K. and G.K.). In the case of G.K., the pathological study led us to conclude that this state may be caused by predominantly unilateral damage to the anteromedial thalamus.

The site of the cyst in this case was such that it would produce the greatest pressure effect in the region of the foramina of Monro, although more marked on the left side. Anatomically the foramina of Monro are bounded postero-laterally by the anteromedial portions of the thalamus. However, there may have also been some pressure exerted on the anterior walls of the hypothalamus below.

Summary of Case J.T.

A case of akinetic mutism and profound impairment of consciousness is described, resulting from a haemorrhagic cyst causing pressure on the anterior diencephalon, particularly in the region of the foramina of Monro. The localising nature of the symptoms was sufficient evidence to suspect a lesion of the third ventricle and thalamus.

CASE J.B.

Involvement of the diencephalon by a parotid gland tumour.

J.B. was a male machinist of 62 years of age at the time of his death on February 5, 1946. His complaints began in 1910, when he noticed a mass in front of the left auricle. Four years later the mass had grown to the size of a walnut, and a local excision was made. Local recurrences were removed in 1919 and 1934, and a diagnosis of mixed tumour of the parotid gland was made.

In 1935, the patient began to have double vision and pain over the left forehead, and in 1937 sensory paralysis of the left side of the face and ptosis of the left eyelid developed.

The patient was referred to the Montreal Neurological Institute for the first time on July 21, 1938, by Dr. Wyllie of Kingston, Ontario. On physical examination at this time, J.B. appeared rational, orientated and intelligent. He cooperated well and appeared emotionally balanced. Proptosis and ophthalmoplegia of the left eye and scarring of the left cornea were present. Sense of smell and hearing acuity were intact, and there was no abnormality of cranial nerves 9 to 12. Deep reflexes, motor system and bodily sensation were unimpaired.

Radiographic examination of the base of the skull on July 26, 1938, showed a large area of bone destruction involving the base of the left middle cranial fossa. The lateral portion

of the left sphenoid sinus was invaded and its walls destroyed, and a soft tissue mass appeared to project into the lateral part of the left sphenoid sinus.

On July 27, 1938, ligation of the left external carotid artery and a left temporal craniotomy with partial removal of the tumour were performed by Dr. Penfield. At operation the tumour presented toward the medial side of the middle cranial fossa; it was covered by a capsule. There was some extension forward into the orbit. J.B. was discharged on August 14, 1938.

Microscopic examination of the surgical specimen showed pure neoplasm consistent with the diagnosis of cylindroma of the parotid gland. The cells were globular, the nuclei dark and round. There were cystic areas, and some alveolar structures were seen.

Following this operation, the patient did remarkably well until June, 1945; at this time his wife noticed an increasing loss of memory and mental dullness. She observed that he had increasing difficulty in finding words and giving expression to them. She stated that at first he would see people and objects and know what they were, but he would be unable to name them.

On November 14, 1945, the patient temporarily lost consciousness and remained in a semi-stuporous condition until his second admission to the Montreal Neurological Institute on November 30, 1945.

On admission examination, the patient appeared dull, confused, and responded poorly to questions. He was not orientated to time and place. Another examiner stated that the patient was drowsy and it was hard to keep his attention.

There was no vision in the left eye, and a temporal hemianopsia in the right eye. There was no pupillary reaction in the left eye, but the right pupil constricted to light. There was complete paralysis of the left cranial nerves 3 to 7.

There was no loss of motor power, coordination or bodily sensation. The reflexes were normal.

The blood serology was repeatedly negative. The blood pressure was 120/76, pulse 80, and both remained constant.

The apparent aphasia was carefully analysed by Dr.Robb. J.B. could recognise a key but failed to name anything else, either by sight or touch. There was no dysarthria associated with the words he spoke. He could repeat simple and difficult words such as "horse" and "British constitution", but his spontaneous utterances made little sense.

He showed an adequate response when asked if he wanted to get well, but he was unable to read, to copy correctly, and to recognise numbers.

He carried out simple commands such as squeezing the hand and touching his nose, but was unable to touch his left ear with his right hand and to put out his tongue on command.

When shown a fountain pen, he said it was a "pencible",

He was unable to name his home town or street, but when Montreal was named together with Toronto and Hamilton, he correctly repeated Montreal. He was unable to carry out simple mathematical problems.

On December 5, a ventriculogram was performed, which demonstrated a displacement of the anterior portion of the third ventricle and septum pellucidum 3 to 4 mm. to the right of the midline. The third ventricle was moderately dilated, with a filling defect in its left inferior portion extending slightly across the midline. The tumour appeared to be growing up from the floor of the left middle fossa. Its lateral border seemed to be at the level of the insula; medially it lay close to the left wall of the third ventricle.

A left subtemporal myoplastic craniotomy was performed by Dr. Penfield, with a further removal of the tumour on December 4, 1945. The tumour lay on the medial wall of the middle fossa, covering the fifth nerve, sella turcica, and orbital fissure, and extended upwards as far as the clinoid processes and possibly higher.

The patient progressed favourably after operation, and twelve days postoperatively, although his state of mental confusion was still severe, he was able to count fingers. On February 3, 1946, a progressive thrombophlebitis developed in the right leg, and the patient died on February 6, 1946, of pulmonary embolism.

Necropsy

The general autopsy demonstrated the fatal embolus in the pulmonary artery; there were no other significant observations, excluding the nervous system.

The brain weighed 1540 grams. There was generalised arteriosclerosis of the circle of Willis. Over the base of the brain there lay a mass of tumour extending from behind the internal carotid artery to just in front of the pons. There was compression of cranial nerves 3 to 7 on the left side.

The tumour had invaded the sphenoid sinus from below and the lateral wall was almost completely destroyed.

The left tip of the temporal lobe of the brain was absent (this removal had been made during the second operative approach to the tumour), and was covered by thickened dura.

The tumour overlay the left mammillary body, optic tract and chiasma, and extended to the midline where it lay in close relation to the infundibulum.

On sectioning the brain, it was apparent that the tumour had entered the left wall of the third ventricle by direct extension through the region of the left mammillary body and the anterior limb of the internal capsule. In the third ventricle it had displaced the

septum pellucidum and fornix to the right. The tumour superiorly had become cystic and had eroded the medial nucleus of the left thalamus as high as the foramen of Monro. The infundibulum was displaced to the right but did not appear to be invaded by tumour growth. (See Fig.14.)

Serial sections were made of the diencephalon in the coronal plane and representative sections stained by the Weigart-Pal method for myelin and hematoxylin for cytological studies.

Microscopic study showed that the floor of the third ventricle had been widely separated by the tumour growth with lateral displacement of the left cerebral hemisphere and widening of the inferior portion of the third ventricle.

The tumour had infiltrated the left wall of the third ventricle and had formed a large cyst which was walled by a mesodermal-glial reaction. The left thalamus had been displaced backwards and the cyst extended from the sub-thalamic region below to involve the dorsomedial and nuclei of the midline above, but had not involved the anterior nuclear group. The mammillo-thalamic tract had been displaced laterally.

The main destruction appeared to be in the nuclei of the midline and the dorsomedial nucleus of the left side.

The fasciculus lenticularis, posterior limb of the internal capsule, intralaminar nuclei and lateral nucleus of the thalamus were not involved. The pes pedunculi and

Fig. 14

Case J.B.

Coronal section of brain at the anterior thalamic level showing entry of tumour into the left medial wall of the third ventricle.

substantia nigra below the cyst remained undamaged. There was some involvement of the posterior hypothalamic region and destruction of the inferior portion of the anterior limb of the internal capsule of the left side.

There was a nodule of tumour involving the left mammillary body which had been displaced to the left. There was another nodule of tumour in the region of the zona incerta.

The left optic tract showed complete degeneration of myelin, but the anterior commissure, although sharply angulated above the tumour, appeared intact.

Summary of Pathological Study

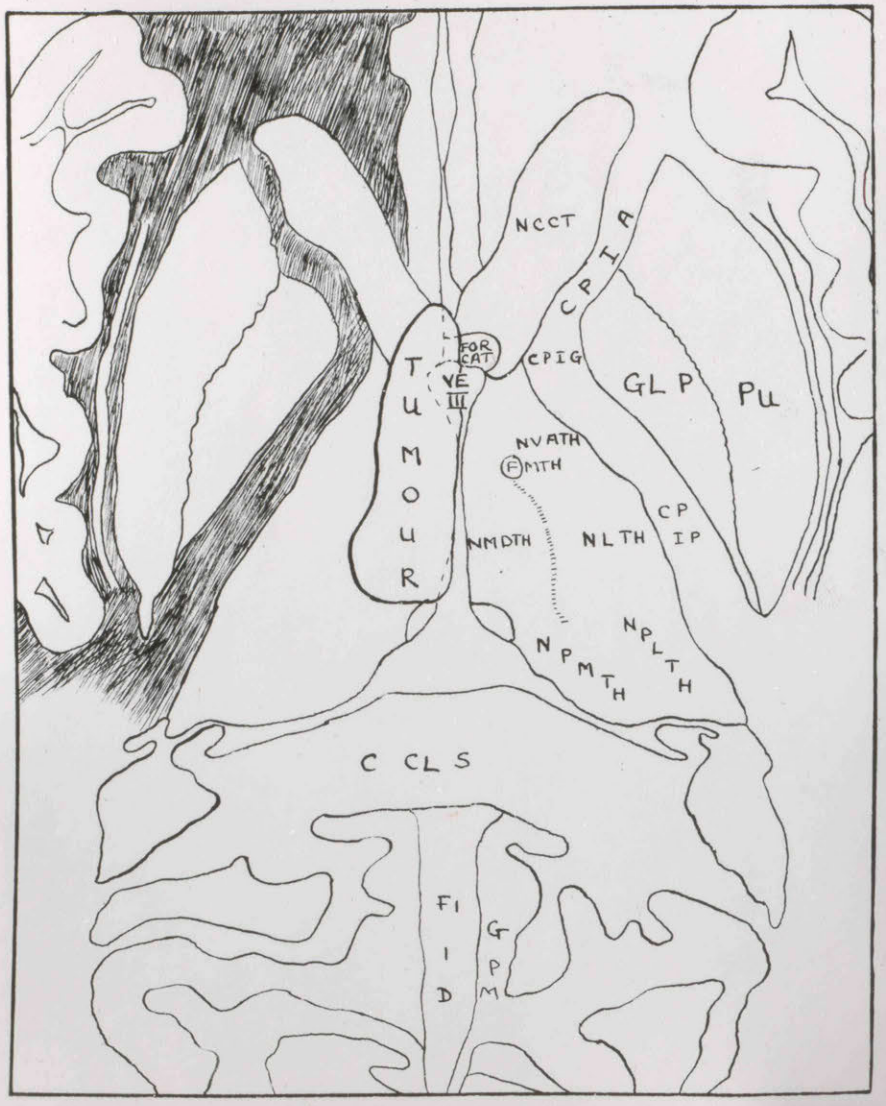
A solid growth of tumour had entered through the flow of the third ventricle in the region of the mammillary body on the left side. The tumour had become cystic superiorly.

There was destruction of the left mammillary body and damage to the immediately adjacent hypothalamus, the left dorsomedial nucleus and nuclei of the midline and the left anterior limb of the internal capsule. The pyramidal system was intact. (See Fig. 15.)

Analysis of Case J.B.

Following the intracranial extension of a parotid gland tumour in the region of the floor of the third ventricle, this patient demonstrated the gradual onset of an unusual symptomatology consisting of:

1. Progressive loss of memory, drowsiness and confusion, a syndrome which is best termed "amentia", if we define this term to mean "a mental disorder characterised by



Case J.B.

The site of the tumour at necropsy. The extent of the tumour has been superimposed on a horizontal section through the diencephalon at the level of the superior end of the mammillo-thalamic tract.

CP I A	Capsula interna crus anterius
CP I G	Capsula interna genu
CP I P	Capsula interna crus posterius
C CL S	Corpus callosum, splenium
FI I D	Fissura interhemisphaerica pars dorsalis
F M TH	Fasciculus mammillo-thalamicus
FOR CAT	Fornix columna anterior, pars tecta
G P M	Gyri parietales mediales
N C CT	Nucleus caudatus, caput
N L TH	Nucleus lateralis thalami
N M D TH	Nucleus medialis dorsalis thalami
N P L TH	Nucleus pulvinaris lateralis thalami
N P M TH	Nucleus pulvinaris medialis thalami
N V A TH	Nucleus ventralis anterior thalami
VE III	Ventriculus tertius

After Riley (1943)

mental confusion of varying degree, sometimes so severe as to approach stupor". (Dorland, 1946)

2. Impairment of speech.

1. Progressive "amentia".

This lesion was manifestly a unilateral destruction of the left posterior hypothalamus, left midline nuclei and left dorsomedial nucleus of the thalamus.

It seems well established that lesions of the thalamus can give rise to personality disorders and evidences of an organic psychosis (Glaser, 1929; Smyth and Stern, 1938; Stern and Dancey, 1942). There is also clinical and experimental evidence that hypothalamic lesions may give rise to similar symptoms (Fulton and Ingraham, 1929; Alpers, 1940). In this case it is impossible to conclude whether the hypothalamic or thalamic lesion was responsible for these changes. But the absence of other hypothalamic symptoms such as loss of temperature control, obesity, diabetes insipidus and hyperphagia tend to incriminate the thalamus. Furthermore, the symptomatology is strikingly similar to the case of progressive drowsiness, confusion, and dementia associated with a glioma of the massa intermedia described by Smyth and Stern (1938).

The component of drowsiness in J.B. may be accounted for by the hypothalamic damage or by damage to the periventricular fibre system and the nuclei of the midline.

The importance of the latter system has already been discussed in our analysis of G.K. In either case an essentially unilateral lesion must have been responsible for the production of symptoms. If the hypothalamic injury was responsible it would not be in exact accord with the experimental findings of Ranson (1937, 1939) in lower animals whose evidence indicated that a bilateral lesion was necessary to produce hypersomnolence.

2. Impairment of speech.

The impairment of speech, without dysarthria, in this case cannot be classified under our present concept of aphasia. The speech difficulty seems to have arisen simultaneously and progressed with the degree of amentia, which suggests that this was a manifestation of the general state of mental deterioration. He could utter simple words and answer elementary questions but any attempt at speech involving any complex neural processes was not forthcoming.

Summary of Case J.B.

A case of progressive amentia and impairment of speech in a case of unilateral involvement of the diencephalon by a parotid gland tumour is described. It is concluded that unilateral damage to the medial thalamus and mammillary region of the hypothalamus accounted for this syndrome.

B. DIENCEPHALIC ABLATIONS IN THE CAT AND THE MONKEY

The pathological study of the series of four lesions in man indicated that damage to the anteromedial portion of the thalamus and mammillary region of the hypothalamus resulted in states of impaired consciousness, therefore this region of the diencephalon was chosen for study by ablation methods in animals.

Results of studies on 23 cats and 2 monkeys fall into three groups which may be listed as follows:

1. A group of 3 control animals which showed no abnormal behaviour following implantation of the electrolysis electrodes in the diencephalon without producing an electrolytic lesion.
2. A group of 15 experimental animals which demonstrated marked behavioural changes consisting of akinesis, apathy, catalepsy, unconsciousness and allied states following ablations in certain specific areas of the diencephalon; these changes usually being associated with electroencephalographic abnormality.
3. A group of experimental animals which showed either slight or no behavioural changes following ablations in other areas than those made in the second group and which showed no electroencephalographic abnormalities.

1. Control Group

This group comprised three cats which underwent identically the same procedure as the other experimental animals except that no electrolytic lesion was made. The electrodes were placed in the thalamus, cemented to the skull and left in place for several days. There was no abnormality of the postoperative electroencephalogram. The animals were examined for the first few days postoperatively during which time no change in behaviour was observed. The electrodes were inserted in a vertical direction. These animals were used later in another series of experiments for thalamic stimulation.

Anatomical placement of the electrodes was as follows:

Cat P8 240. Needle points were placed in the left anterodorsal and left anteroventral nuclei.

Cat P8 345. Needle points were placed in the left anteromedial and left anteroventral nuclei.

Cat P8 356. The needle points were placed in the nucleus centralis medialis and the right nucleus centrum medianum.

2. Group showing marked behavioural changes consisting of apathy, akinesis, catalepsy, unconsciousness and similar states.

Anatomical analysis of this group of animals suggests that they may be subdivided into a further three groups:

(a) Consists of 9 cats with lesions involving the anterior nuclei of the thalamus and the terminal end of the mammillo-thalamic tract.

(b) Consists of 2 cats and 1 monkey with thalamic lesions in the region of the middle of the mammillo-thalamic tract and nuclei of the internal medullary lamina.

(c) Consists of 3 cats with unilateral and bilateral lesions of the mammillary bodies and hypothalamic portion of the mammillo-thalamic tract.

Summaries of the protocols will be given.

(a) Damage to the anterior nuclei and the termination of the mammillo-thalamic tract.

CAT P8 229

Postoperative Behaviour

Eighteen hours after operation the animal lay on its side with its eyes open without spontaneous movement. On painful stimulation there was movement of the tail, and on pricking the ears the head was shaken. The animal swallowed milk placed in its mouth and licked its whiskers, but would not feed spontaneously. When undisturbed the animal remained immobile. The righting reflexes were intact and there was no abnormal tone or reflexes. When stimulated energetically and placed on its feet the animal walked several steps slowly

forward until its head struck the wall and remained immobile in this position until it collapsed.

In spite of forced feeding the animal died on the third postoperative day.

Electroencephalography

Immediately postoperatively the electroencephalogram showed random slow background activity and occasional slow waves of a frequency between 2 to 4 cycles per second.

Pathological Study

There was slight herniation of the cortex through the skull defect on opening the dura. The lesion was larger than anticipated, involving the rostral portion of the corpus callosum, stria medullaris, the nucleus paraventricularis anterior, the nucleus rhomboideus, the nucleus centralis medialis, the medial portion of the nucleus dorsalis medialis with complete destruction of the anterior nuclear group and the terminal fibres of the mammillo-thalamic tract. There was also damage to the habenular nuclei and the habenulo-peduncular tract.

CAT P8 235

Postoperative Behaviour

Immediately after operation the respirations of this animal became slow and a total of 1.15 cc. of picrotoxin were given intravenously over a fifteen minute period. Respirations

became satisfactory but there was no motor response. Twenty-four hours postoperatively the animal made no spontaneous movement but would maintain a crouch position if placed in it. There was a tendency to maintain abnormal postures.

Two days postoperatively the animal had not taken his feedings but it was noted that on administering intragastric fluids there was snapping and hissing as the tube was passed. There was no spontaneous movement, but the eyes were open and followed moving objects. Pilo-erection was noted over the shoulders and back, and the heart rate was very rapid (210 beats per minute).

Four days postoperatively the apathetic and akinetic state was unchanged and it was noted that the hopping and placing reflexes were intact. (See Fig. 16.)

On the fifth postoperative day the animal was placed on a platform one foot square where it remained 12 hours without evidence of change of position.

Six days postoperatively when dropped from a height of one foot to the ground the animal walked slowly to a corner where it assumed a crouch position without further movement.

On the eighth postoperative day the animal's coat was soiled in spite of frequent brushing. She would not feed spontaneously, but would walk several paces on painful stimulation.

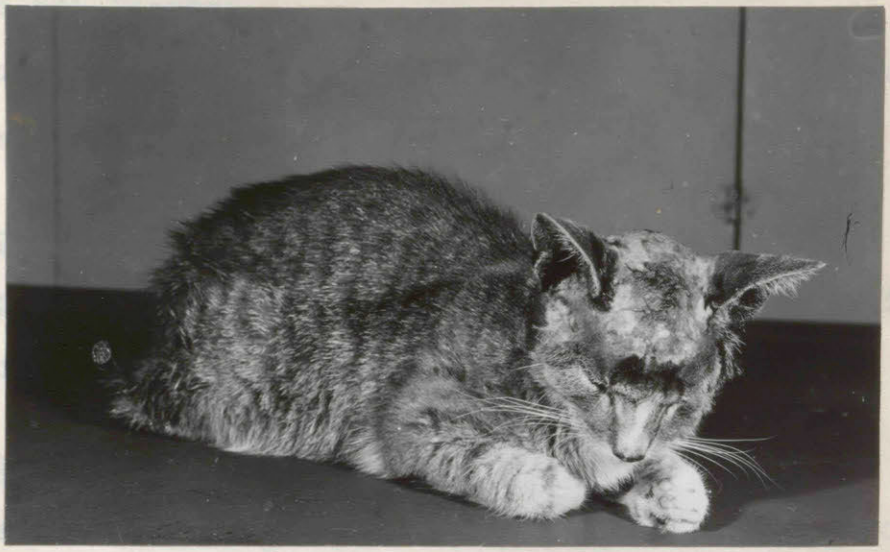


Fig. 16

Cat P8 235

Still photograph taken four days after the lesion was made. The pilo-erection was continually maintained, and the animal remained constantly crouched in this posture with head drooping but eyes open for hours at a time with no spontaneous movement.

On the thirteenth day after operation the cat drank milk from her bowl for the first time. Her meat ration, however, was not touched.

The animal was sacrificed on the fifteenth postoperative day when she still presented a markedly akinetic state.

Electroencephalography

Postoperative records showed intermittent periods of slow wave activity at 3 to 4 cycles per second.

Pathological Study

The lesion was small and well-localised, confined to the anterior thalamic nuclei and the terminal fibres of the mammillo-thalamic tract. There was some damage to the stria medullaris, the nucleus parataenialis, and the nucleus rhomboideus. (See Fig. 17.)

CAT P8 237

Postoperative Behaviour

The animal was found lying on its side on the first postoperative day. The eyes were open and followed moving objects. When placed on its feet the animal slowly assumed a crouch posture and would not move from this attitude.

For the next few days the animal did not feed and made no spontaneous movement except occasional postural changes. No rage reaction or other response could be induced by painful stimulation, although occasionally the animal

Fig. 17

Cat P8 235 Weil (X7)

Illustrating bilateral lesions in the region of the anterior nuclear group of the thalamus.

would progress a few steps with a slow, crouched gait.

On the sixth postoperative day it was noted that the animal was completely passive when picked up and could be maintained in abnormal postures without struggling or attempting to resist. When dropped, however, the righting reflexes could be demonstrated to be intact.

On the tenth postoperative day the animal drank its milk spontaneously for the first time, and the next day when placed on the floor the animal walked several paces to the corner of the room where it remained quietly in a crouched posture. The hopping and placing reactions were intact.

On the twenty-fifth day postoperatively the lack of spontaneous activity was still marked. Painful stimuli produced a subnormal response and the animal's reactions appeared subdued and recessive.

Twenty-eight days postoperatively the cat could be held upside down, and in other abnormal postures without resistance or struggling.

Forty days postoperatively there was purring on stroking the animal, raising of the tail and rubbing of the body against the examiner. No rage reaction could be elicited, however, by pinching and pulling the tail and holding the animal in abnormal postures.

Without stimulation the animal retained one posture for prolonged periods.

These abnormalities, together with a marked neglectfulness of grooming, could be demonstrated until the sixty-fifth postoperative day when the animal was sacrificed.

Pilo-erection over the back and a rapid heart rate of over 200 beats per minute were repeatedly found on the day to day examination.

Electroencephalogram

The immediate postoperative electroencephalogram was characterised by generalised intermittent slow wave activity, at 2 to 3 cycles per second, more marked in right temporal regions. Records taken without anaesthesia on the fourth and sixth days postoperatively showed generalised, continuous 3 per second slow wave activity, with rare 6 per second bursts. Metrazol (0.5 cc. intravenously) and painful stimulation produced some delta rhythm but the rhythmic slow activity returned almost immediately. (See Fig. 38, p. 126b)

Pathological Study

There was bilateral destruction of the anteromedial, anterodorsal and midline nuclei anteriorly, with damage to the anterior portions of the dorsomedial nuclei on both sides. The superior portion of the mammillo-thalamic tract was interrupted. (See Fig. 18.)

Fig. 18

Cat P8 237 Weil Stain (X7)

Illustrating bilateral damage to the anterior nuclear group of the thalamus in the region of the termination of the mammillo-thalamic tract.

CAT P8 343

Postoperative Behaviour

On the first postoperative day the animal was found curled in the cage with his eyes open. On repeated stimulation the animal moved as though he was about to rise to his feet but appeared unable to do so.

On the second day the cat remained crouched in its cage with pilo-erection along the trunk and back. The eyes were open and on stimulation there was slow turning of the head. The heart rate was 180 per minute. The pupils were equal and reacted to light. The body temperature was 105° F. per rectum. Placing and hopping reactions were present. The animal would not eat spontaneously and had to be fed intragastrically.

On the third postoperative day the animal was found dead in its cage. The cause of death was considered to be hyperthermia.

Electroencephalography

The electroencephalogram was characterised by random slow wave activity of 1 to 3 cycles per second which was more marked on the left side.

Pathological Study

There was unilateral damage to the nucleus anteroventralis, nucleus anterodorsalis and nucleus anteromedialis.

The terminal fibres of the mammillo-thalamic tract were damaged on the left side. There was some damage to the anterior portion of the nucleus lateralis on both sides.

CAT P8 352

On the first postoperative day the animal was found lying in its cage. On stimulation the animal opened its eyes but could not respond. It could be propped up into a crouch position, but tended to lie on its side. The animal could not feed itself.

On the second postoperative day the animal remained in a crouch posture without any spontaneous movement. The pupillary and righting reflexes were normal, and hopping and placing reactions were intact. There was pilo-erection of the back and trunk. The temperature was 103.8° F. (See Fig. 19).

On the third postoperative day the animal's akinetic state was unchanged and it had to be force fed. The temperature was 104° F. In the evening the animal was photographed under strong lights and died as it was returned to its cage. It was concluded that the cause of death was hyperthermia.

Electroencephalographic studies were not made in this animal.

Pathological Study

There was bilateral damage to the anteromedial and dorsomedial nuclei and to the terminal fibres of the mammillo-thalamic tract. (See Fig. 20.)

Fig. 19

Cat P8 352

Still photograph taken three days after the lesion was made. The pilo-erection was continually maintained, and the animal remained constantly crouched in this posture with head drooping but eyes open for hours at a time with no spontaneous movement.

Fig. 20

Cat P8 352 Weil Stain (X7)

Illustrating damage in the region of the anteromedial nuclei of the thalamus.

CAT P8 364

Postoperative Behaviour

At the close of operation, which was carried out with minimal blood loss, it was noted that the heart rate was so rapid it could hardly be counted but was estimated to be 320 beats per minute. The respirations were 40 per minute and the temperature was 103.2° F. Pilo-erection was present.

Within four hours the temperature rose steadily to 104.6° F. and a fan was played over the animal. Eight hours later the temperature was 103.4° F. The heart rate varied between 232 to 250 per minute. When the fan was turned off for ten minutes the temperature rose again to 104° F.

On the first postoperative day the animal showed a slow clonic movement of the head from side to side. It remained constantly in a crouch posture with the head hanging low, but the eyes open. This posture was maintained constantly if undisturbed. Hopping and placing reactions were present, and painful stimulation produced a slow withdrawal of the limbs. The animal had to be force fed. When placed on a stool with its head hanging over the edge, it remained this way for several minutes before withdrawing its head. The animal showed no interest in its environment whatsoever.

Behaviour remained unchanged and it was noted on the sixth postoperative day that the temperature was now 102°F.

The heart rate was still rapid at 228 per minute. The cat's fur was now matted with excreta, food and sawdust.

On the seventh day postoperatively the temperature returned to its preoperative reading of 99° F., and piloerection was no longer present. The heart rate, however, was over 200 beats per minute. Righting reflexes and hopping and placing reactions were intact. On pinching the tail the animal whined softly but made no movement.

Eight days postoperatively the animal was weighed and had lost 700 grams in spite of intragastric feeding. The animal could not be made to change his position by any form of stimulation.

On the tenth postoperative day the animal drank from its milk bowl for the first time. The next day it ate hungrily when meat was given to it. On repeated stimulation the animal could be made to walk several paces with an unsteady gait before settling down to its customary posture. No rage reaction could be elicited.

The animal's behaviour remained unchanged and it was still akinetic when sacrificed on the sixteenth postoperative day.

Electroencephalography

Electroencephalograms taken four days after operation without anaesthesia were characterised by periods of decreased amplitude in activity, giving a rather flat type of record.

The record had many of the similarities of profound barbiturate anaesthesia.

Pathological Study

There was extensive damage to the anterior nuclear group of the thalamus, the superior portion of the mammillo-thalamic tract, the dorsomedial nuclei and the anterior portion of the lateral nuclei on both sides. There was some damage to the habenular nuclei and the lateral nuclei of the pulvinar.

CAT P8 373

Postoperative Behaviour

On the first postoperative day the animal was found lying full length in its cage with its eyes closed. The animal could not be aroused by painful stimulation but there was withdrawal of the limbs. The eyes would open with stimulation and the pupils reacted to light. The tone and reflexes were normal, and sluggish righting reflexes could be elicited. There was no pilo-erection; the temperature was 100.6° F., and the heart rate was 210 beats per minute. When the limbs were placed in abnormal postures there was very sluggish withdrawal, there being some elements of catalepsy. When left alone the animal made no spontaneous movement whatsoever.

On the second postoperative day the animal assumed a crouch posture which it maintained almost constantly without change. The temperature was 102.6° F. and the heart rate was 214 beats per minute. The respirations were 26 per minute. (See Fig. 21.)

The animal's behaviour remained unchanged on the third postoperative day, but on repeated stimulation it walked several paces in a slow, lethargic manner. The animal was sacrificed after electroencephalographic study.

Electroencephalography

On the third postoperative day electroencephalographic records were made without anaesthesia and showed occasional 3 per second slow wave activity more marked on the left side.

Pathological Study

Anteriorly there was damage to the septum pellucidum. More posteriorly the medial fibres of the mammillo-thalamic tract, the anteromedial nuclei, dorsomedial nuclei, nuclei of the midline and intralaminar nuclei of the thalamus were damaged.

CAT P8 379

Postoperative Behaviour

On the first postoperative day the temperature was 103.4° F., the heart rate 240 beats per minute and the respirations were rapid at 36 per minute.

Fig. 21

Cat P8 373

Photograph taken on the third postoperative day. The animal maintained this posture for long periods without movement if left undisturbed.

The animal was quiet but not to the same degree as the other animals in this group. On repeated stimulation she would walk slowly and purred on stroking.

On the second day postoperatively there was pilo-erection over the back and forelimbs. The heart rate was 248 per minute but the body temperature was not elevated. The animal would purr on stroking.

The animal was sacrificed on the third day post-operatively.

Electroencephalography

The immediate postoperative record showed no change from the preoperative control. Occasionally there was some slow background activity but it was not marked.

Pathological Study

There was damage to the septum pellucidum and anterior columns of the fornix. There was bilateral damage to the anteromedial nuclei of the thalamus more marked on the left side and there was some damage to the anterior portion of the dorsomedial nucleus. The anteroventral nuclei and the mammillo-thalamic tract were intact bilaterally.

In the general autopsy examination it was noted that there was a superficial erosion of the gastric mucosa (1 cm. in diameter) on the greater curvature of the stomach. (See Fig.22)

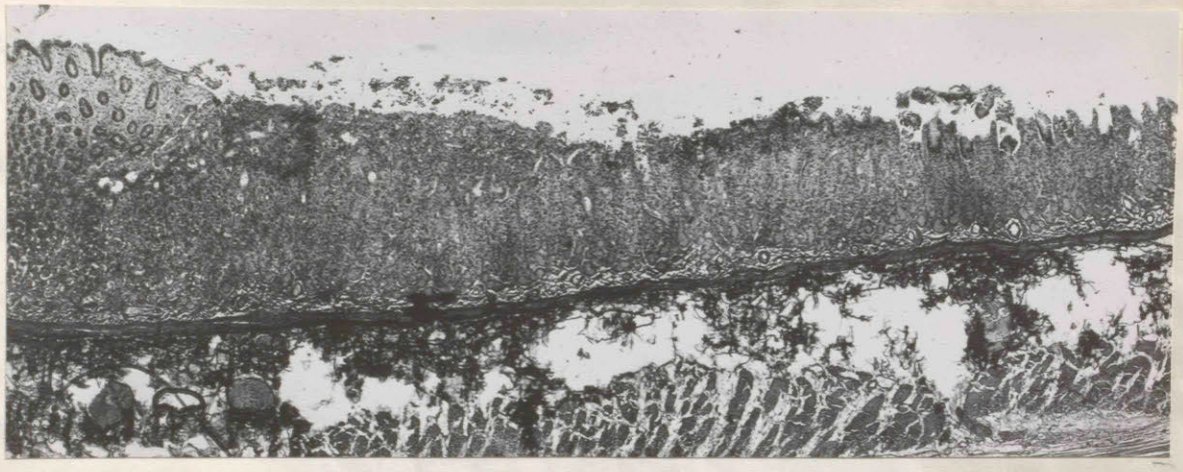


Fig. 22

Cat P8 379 Hematoxylin Eosin (X40)

Low power view of the mucosal erosion found in the greater curvature of the stomach of this animal following a lesion in the region of the anterior nuclei of the thalamus.

CAT P8 387

Electrocardiographic records taken preoperatively showed a heart rate of 160 per minute. Immediately following the lesion the heart rate was 280 per minute. Extrasystoles were present.

Postoperative Behaviour

On the first postoperative day the animal was found crouched in its cage, immobile and unresponsive. The left pupil was larger than the right, and when the right foreleg was placed over the edge of the examining table, the limb was not withdrawn. Pilo-erection was marked over the trunk and spine; the heart rate was 240 per minute and the temperature was 103° F.

The animal's behaviour remained unchanged for seven days postoperatively (Fig. 23). It remained akinetic, with tachycardia and hyperthermia and would not feed spontaneously. The coat became soiled and response to stimulation was lethargic. This animal was not fed by stomach tube and died on the seventh postoperative day.

Electroencephalography

The postoperative record was characterised by generalised slow background activity with occasional random high voltage slow waves at a frequency of 1 to 2 per second.

Fig. 23

Cat P8 387

Photograph taken on the fifth post-operative day. The animal maintained this posture for prolonged periods and showed no spontaneous movement if undisturbed. Pilo-erection was present along the trunk and back.

Pathological Study

There was bilateral symmetrical destruction of the anteromedial nuclei and the terminal fibres of the mammillo-thalamic tract. There was damage to the stria medullaris, and nucleus centralis lateralis and the anterior portion of the nucleus lateralis.

(b) Damage to the midportion of the mammillo-thalamic tract and the nuclei of the internal medullary lamina.

CAT P8 383

Postoperative Behaviour

This animal lived only two days postoperatively. During this period the animal showed the features of catalepsy (Ingram, Barris and Ranson, 1936). It could be moulded into abnormal postures which it would maintain for prolonged periods. The muscle tone, however, was not increased. Response to auditory and tactile stimulation could not be elicited, but there was a response to moving objects placed in front of the eyes.

The animal was seen to walk several paces on two occasions. The movements were extremely slow and lethargic. On the first occasion the animal walked off the examining table and on the second occasion the animal walked into a wall, where it stopped and remained motionless. The temperature was 102^{o} F. and the heart rate was 260 per minute.

Electroencephalography

The immediately postoperative record was not markedly abnormal. There was some questionable slow background activity, but owing to a poor preoperative record further interpretation was not possible.

Pathological Study

The midportion of the mammillo-thalamic tract was severed. There was partial damage to the following nuclei: ventralis anterior, reuniens, arcuatus, centralis medialis, rhomboideus and anteromedialis.

CAT P8 396

Postoperative Behaviour

Following operation this animal's temperature was 105° F. and the heart rate was over 200 per minute. The animal was quite akinetic when left alone.

Catalepsy was extremely marked in this animal although there was no increase in muscular tone. It would spontaneously assume statuesque attitudes which it would maintain for prolonged periods of time and all four limbs could be moulded into abnormal postures which were readily maintained (Figs. 24, 25, 26 and 27).

The autonomic and locomotive abnormalities persisted until the animal died five days after operation following prolonged exposure to photographic lighting. The cause of death was thought to be hyperthermia.

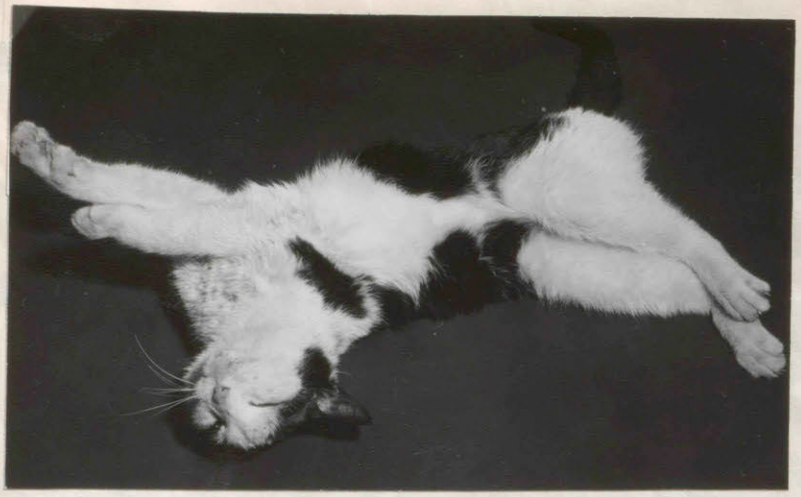


Fig. 24

Fig. 25

Fig. 26

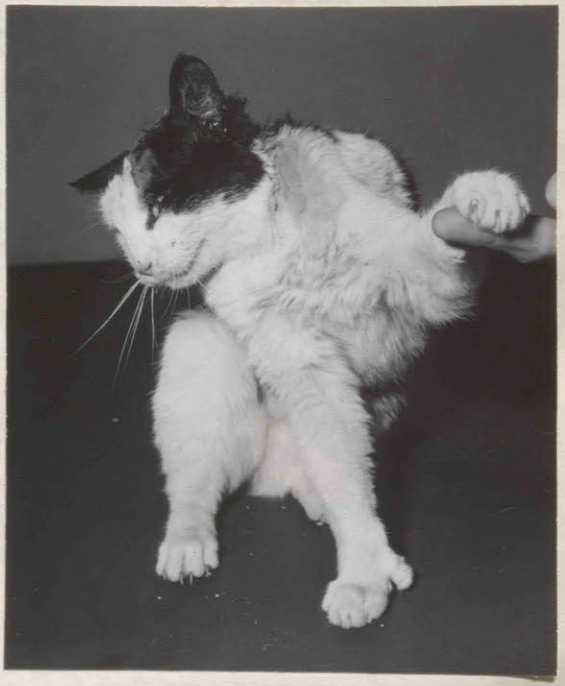


Fig. 27

Cat P8 396

Catalepsy in a cat with a thalamic lesion. These attitudes were maintained for prolonged periods following ablation of the midportion of the mammillo-thalamic tract and intralaminar nuclei.

Electroencephalography

No change could be discerned between the preoperative and postoperative records.

Pathological Study

The lesion extended from the anterior nuclear group of the thalamus to the pulvinar. The nucleus reuniens was destroyed throughout. There was marked damage to the nucleus centralis medialis and nucleus centralis lateralis bilaterally (Figs. 28 and 29).

The medial fibres of the mammillo-thalamic tract were destroyed, and there was damage to the nucleus dorsalis medialis on both sides.

MONKEY P8 412

This monkey has had small lesions placed in the region of the mammillo-thalamic tract on three occasions. He has been observed for three and a half weeks. Following the first operation the animal became quiet and more easy to handle. He tended to remain on the floor of the cage more than the unoperated controls. He showed none of the playfulness of normal monkeys and there was a marked absence of facial grimacing. Pilo-erection was marked over the back and fore-limbs.

On the first two postoperative days there were myoclonic seizures involving all four limbs while the head was turning

Fig. 28

Cat P8 396 Weil (X7)

Illustrating the lesion in the anterior portion of the thalamus in the region of the intralaminar nuclei.

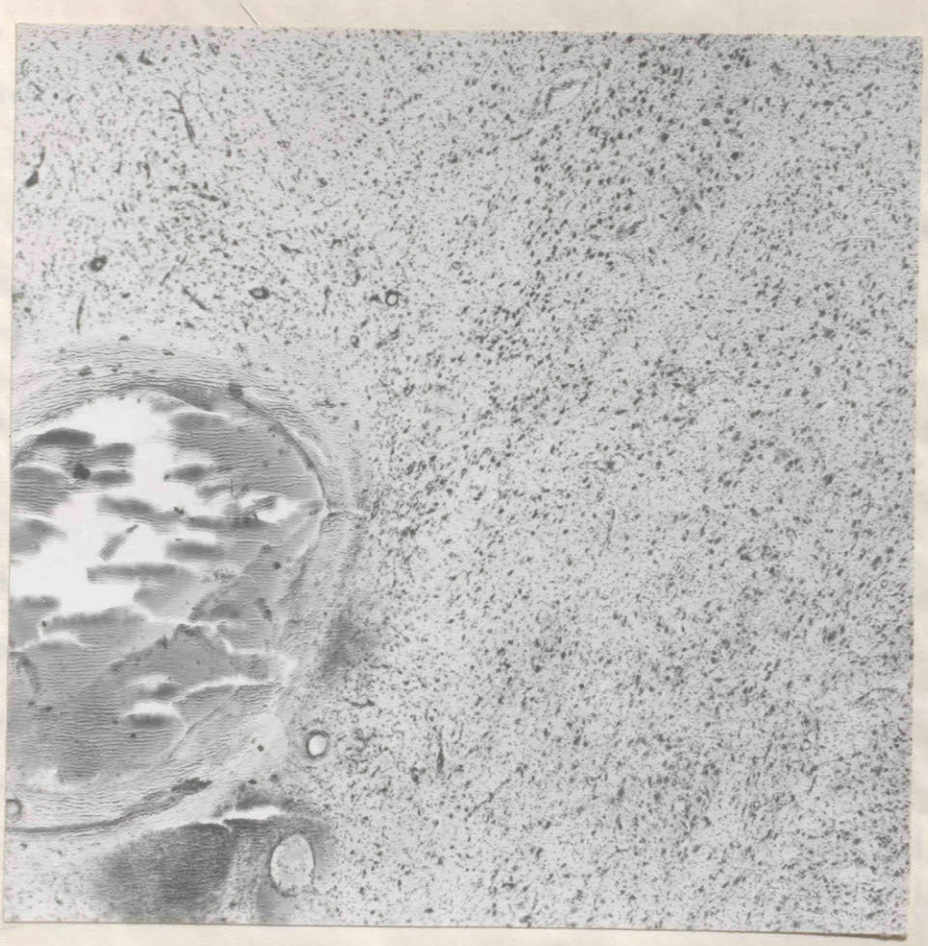


Fig. 29

Cat P8 396 Nissl (X40)

The lesion is located in the nucleus centralis medialis. The dark band of cells superior and lateral to the lesion is the nucleus centralis lateralis.

back. Following these seizures the animal became very subdued.

Two reoperations have been performed on this animal and further lesions made in the same region but no other change has been noted. The seizures have ceased and the animal feeds himself almost continuously. He remains a docile, expressionless monkey with a marked absence of playfulness and is being retained for further study.

Electroencephalography

Immediately following the first operation the record was characterised by random slow waves between 2 to 4 cycles per second, these waves occasionally showing a sharp front.

On repeated examination this animal has shown records varying from normal alpha activity to delta activity between 3 to 4 cycles per second. Curiously, the record frequently changes from alpha to delta activity with stimulation and the slow activity persists with struggling (this being a complete reversal of the normal sequence).

(c) Unilateral and bilateral damage to the mammillary bodies and inferior portion of the mammillo-thalamic tract.

CAT P8 395

Electrocardiograms taken preoperatively showed the heart rate to be 200 beats per minute; immediately following the lesion the heart rate slowed to 170 beats per minute.

Postoperative Behaviour

Following the operation the animal remained profoundly unconscious until it died on the fourth postoperative day. While the animal was alive bradycardia persisted (100 beats per minute) and the body temperature was consistently sub-normal at 95° F. in spite of a warmed cage. The animal remained lying on his side with the eyes half closed and could not be aroused (Fig. 30).

On painful stimulation he would withdraw all four limbs. For the first 24 hours there were attacks of decerebrate rigidity.

He was occasionally seen to wag his tail feebly when fed, and on the third day he held his head up weakly on repeated stimulation. The hopping and placing reflexes were absent, and the deep reflexes were brisk. On pinching the gluteal muscles there were occasional running movements of all four limbs. The claws were continuously extruded on the right side.

It was noted that the animal although blindfolded would salivate and lick his lips when fresh meat was held in front of his nose which was taken as evidence that the sense of smell was intact.

Interpeduncular haemorrhage was suspected because of the brisk reflexes and the occasional attacks of decerebrate rigidity.

Fig. 30

Cat P8 395

Photograph taken three days after ablation of the mammillary bodies.

Electroencephalography

No significant change was observed between the pre-operative and immediate postoperative records.

Pathological Study

A small haemorrhage had occurred from one of the retromammillary arteries. There was a small collection of blood in the interpeduncular subarachnoid space.

The mammillary bodies and mammillo-thalamic tract had been destroyed by the lesion bilaterally and there had been a small haemorrhage in the region of the left habenulo-peduncular tract (Fig. 31).

CAT P8 398

During the operation an excellent response was obtained from cingulate electrodes when the region of the right mammillary body was stimulated (Fig. 32). A small lesion was made on the right side only. Immediately following the lesion the electrocardiogram showed marked slowing compared to the preoperative record.

Postoperative Behaviour

The animal lived for five days following operation but would not feed spontaneously. The animal was akinetic if left alone but if stimulated he would walk slowly in small circles to the right.

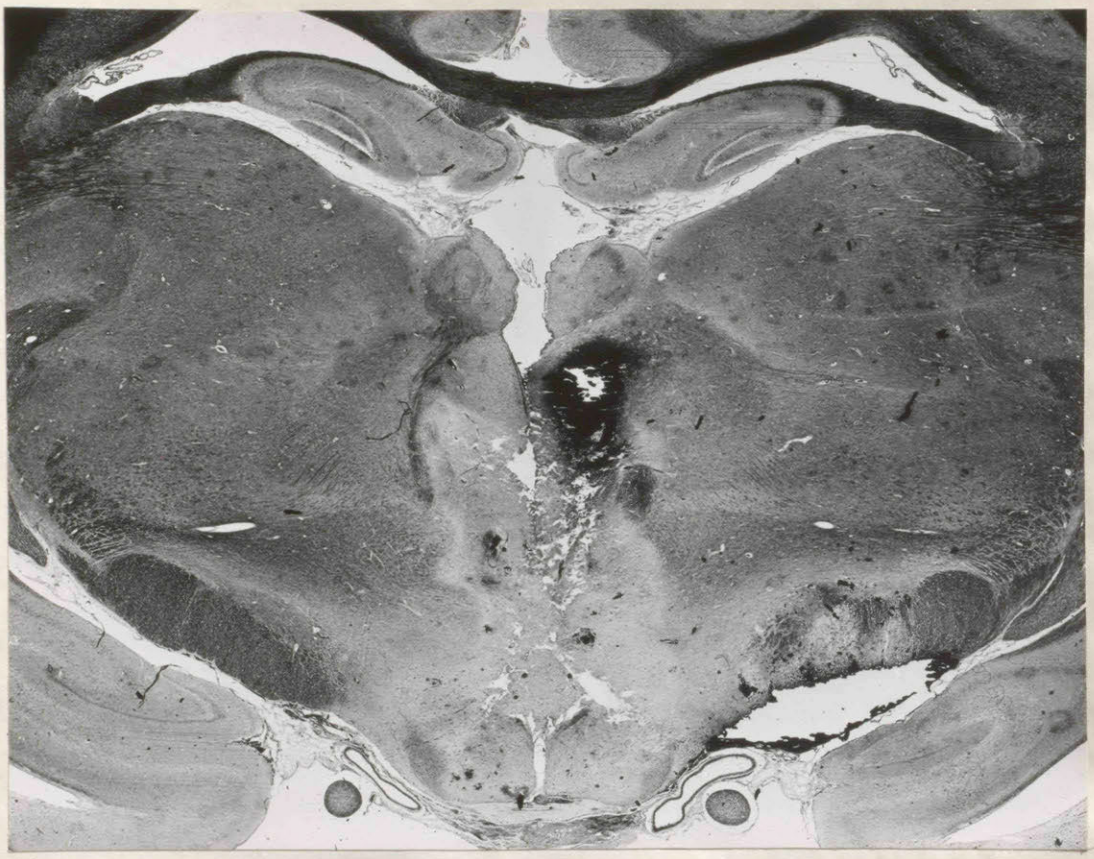


Fig. 31

Cat P8 395 Weil (X7)

Showing bilateral destruction of mammillary bodies and mammillo-thalamic tract. There is an area of haemorrhage in the left habenulo-peduncular tract.

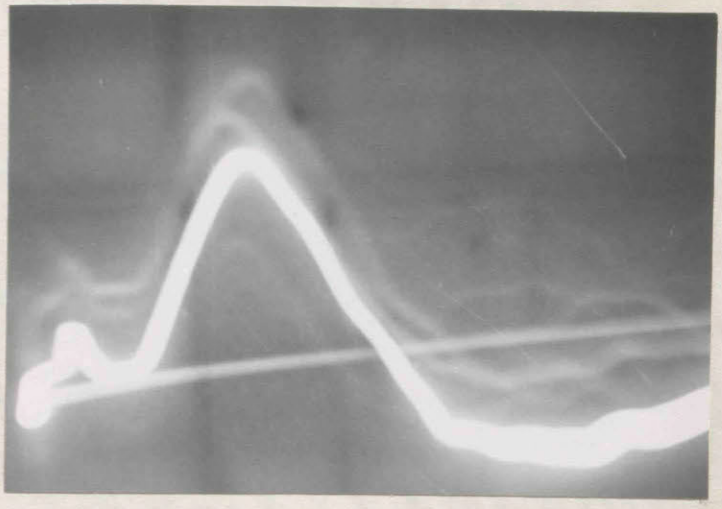


Fig. 32

Cat P8 398

Controlling placement of electrodes. Photograph showing oscillographic recording of a response from the cingulate gyrus following stimulation of the right mammillary body.

The right pupil was dilated more than the left. Bradycardia was marked (128 beats per minute) and the temperature was 102 to 104° F. The animal showed many of the components of catalepsy, and could be placed in abnormal postures which were maintained for several minutes. The animal also assumed statuesque postures spontaneously.

The claws were continually extruded on the right side but not on the left. Hopping and placing reactions and deep reflexes were intact.

Electroencephalography

The postoperative records showed very little abnormality.

Pathological Study

The lesion was extraordinarily well localised. There was destruction located only in the right mammillo-thalamic tract, right mammillary body and adjoining fibres of the fornix. No other neighbouring structures appeared to be damaged (Fig. 33).

No other abnormalities were found at autopsy and the cause of death remained undetermined.

CAT P8 400

Immediately after the lesion had been made the electrocardiogram showed a marked slowing of heart rate.

Fig. 33

Cat P8 398 Weil (X7)

Unilateral damage confined to the right mammillary body and mammillo-thalamic tract. Cataleptic attitudes were maintained by this animal.

Postoperative Behaviour

The animal lived for four days postoperatively. On the first postoperative day the animal was deeply unconscious and could not be aroused. Repeated painful stimulation produced slow withdrawal of the limbs. The pupils were equal.

The temperature varied between 102 to 104.4° F. There was pilo-erection of the back.

On the second postoperative day the animal was found in a crouch posture with the head down and could not be made to walk. Catalepsy was marked but the eyes were open and followed moving objects.

On the fourth postoperative day the animal was found lying on its side, but when moulded into abnormal postures it would maintain them. The animal, unfortunately, aspirated its intragastric feeding and died.

Electroencephalography

There was some random slow wave activity in the postoperative record between 2 to 4 cycles per second. The abnormality was not marked compared to preoperative records.

Pathological Study

Aspirated material was found in the lower lobes of both lungs.

The sections of the brain showed that the lesion was

more marked on the left side than the right. The mammillary bodies had been severely damaged bilaterally. The junction of the mammillo-thalamic tract and the fornix with the mammillary body together with the nucleus hypothalamicus lateralis and nucleus hypothalamicus posterior had been destroyed on the left side.

3. Group showing no marked change in behaviour or abnormal electroencephalographic activity.

CAT P7 99

Postoperative Behaviour

Following the lesions this animal was alert but rather more docile than before the operation. The animal could be handled easily and did not bite or scratch when painfully stimulated. If left alone on the examining table he would quickly jump to the floor.

Pathological Study

There was damage to the midline nuclei of the thalamus. The nucleus reuniens was destroyed and there was destruction of the nucleus hypothalamicus dorsomedialis.

CAT P8 242

Postoperative Behaviour

On the first postoperative day the animal fed itself, groomed its coat and walked around the cage with interest.

There was no marked abnormality of behaviour except that painful stimulation produced less response than in control animals.

Pathological Study

There was extensive destruction of the nucleus dorsalis medialis bilaterally, slight damage to the nuclei of the midline and to the nucleus lateralis pars anterior.

CAT P8 354

Postoperative Behaviour

No change in behaviour could be detected following operation.

Pathological Study

There was bilateral destruction of the nuclei of the midline and stria medullaris and there was bilateral damage to the nucleus lateralis pars anterior and less damage to the nucleus dorsalis medialis on the right side.

CAT P8 369

Following operation the animal was rather less active than previously. Painful stimulation brought little response. The animal walked normally but there was a tendency to maintain one posture for a long time. The animal could not be moulded into abnormal positions.

Pathological Study

There was bilateral damage to the nucleus ventralis posteromedialis, habenulo-peduncular tract and intralaminar nuclei. The lesion bordered the mammillo-thalamic tract on both sides but did not interrupt it.

CAT P8 370

Postoperative Behaviour

Following operation no change could be discerned in this animal except that there was an exaggerated response to painful stimulation, with scratching, hissing and biting (Fig. 34).

Pathological Study

There was bilateral damage to the nucleus lateralis pars posterior and intermedia. The upper portion of the nucleus ventralis posterior was damaged on both sides (Fig. 35). There was slight damage to the lateral pulvinar nuclei and the medial geniculate body of the left side.

CAT P8 388

Postoperative Behaviour

Following operation the animal fed itself and walked around the cage, but appeared to be rather less active than before operation. There was a markedly decreased response to painful stimulation (Fig. 36).

Fig. 34

Cat P8 370

Photograph taken one week after operation. Bilateral lesion of lateral nuclei of thalami. Animal appeared normal except that there was an exaggerated response to painful stimulation.

Fig. 35

Cat P8 370 Weil (X7)

Bilateral lesion involving the lateral nuclei of the thalamus.

Fig. 36

Cat P8 388

Photograph showing decreased response to painful stimulation following bilateral damage to the dorsomedial nuclei of the thalamus.

Pathological Study

There was bilateral damage to the nucleus dorsalis medialis, the stria medullaris, nuclei of the midline and habenulo-peduncular tract.

MONKEY P8 408

Postoperative Behaviour

Unfortunately this animal only lived for one day following operation, but no marked behavioural changes were observed on the first postoperative day.

Pathological Study

There was bilateral damage to the anterior limb of the internal capsule and the anterior portion of the reticular nuclei of the thalamus. There was slight damage to the head of the caudate nucleus on the left side.

The cause of death was intraventricular haemorrhage.

VI. DISCUSSION

A. DIENCEPHALIC DAMAGE IN MAN

The essential nature of consciousness is considered to be a psychological rather than a physiological problem and will not be debated here; however, it is assumed that the function of certain regions of the brain is more closely related to the existence of consciousness than others.

From a clinical viewpoint consciousness is considered to be the normal state of awareness of the synthesis of internal and external stimuli with past experience, which state may be assessed objectively by observing the response to that synthesis and by evaluating the memory of that synthesis. Different degrees of impairment of consciousness may occur.

Thus a patient who is deeply unconscious shows no response to any form of stimulation, shows no interest in his environment, shows no spontaneous activity and on recovering consciousness has amnesia for the period of unconsciousness.

Analysis of the four cases presented has shown that the first three cases (G.K., E.K., J.T.) have such a striking similarity of symptoms that they may most easily be discussed together while the last case (J.B.) will be considered separately.

Cases G.K., E.K. and J.T. show two developments of a remarkable nature:

1. Almost total cessation of speech, absence of spontaneous movement, and profound impairment of consciousness.
2. Electroencephalographic changes with replacement of normal rhythms by very low voltage slow waves especially in parieto-occipital regions and in frontal regions.

1. Almost total cessation of speech, absence of spontaneous movement, and profound impairment of consciousness.

This phenomenon of cessation of speech and absence of spontaneous movement was described by Cairns, Oldfield, Pennybacker and Whitteridge (1941) in their important case of third ventricle cyst as "akinetic mutism". They postulate that the syndrome is due to a primary disturbance in the hypothalamo-thalamic pathways alongside the third ventricle although they could make no pathological study of the exact areas involved. However, they were able to demonstrate on three different occasions (by repeated drainage of the cyst) that this state was readily reversible and that the child had complete amnesia for the period of akinetic mutism.

As in their case, we are able to rule out intracranial tension as a cause of this state in all three of our cases.

In the case of G.K. there was some damage to the lateral nuclear group of the thalamus, but since unilateral lesions of the sensory thalamus have a well defined symptomatology (Dejerin and Roussy, 1906) without akinesis, mutism, or impairment of consciousness, it seems logical that involvement of this area was not the primary factor. Also, in this case (G.K.) section of the corpus callosum was carried out before operation on the third ventricle and following this procedure there was no alteration in consciousness, activity or speech, while in the case of J.T. the state of akinetic mutism developed before operation and section of the corpus callosum. Furthermore agenesis of the corpus callosum is not an infrequent finding without such symptoms (Hyndman and Penfield, 1937).

Transection of the fornix can also be carried out without such symptoms (Cairns, Oldfield, Pennybacker and Whitteridge, 1941).

In the case of G.K. the unilateral destruction of the globus pallidus and slight damage to the putamen, caudate nucleus, red nucleus, and substantia nigra would not account for such a state in the light of most clinical and experimental studies (Wilson, 1940; Mettler, 1942; Kennard and Fulton, 1942; Davison, 1942).

In the case of G.K. the hypothalamus was not injured, and the available evidence suggests that the hypothalamus was not involved in cases E.K. and J.T.

For these reasons it may be concluded that this curious state was caused in the case of G.K. by destruction of the anterior nuclei and nuclei of the midline of the thalamus bilaterally, and unilateral damage to the dorso-medial and intralaminar nuclei and adjacent fibre systems. Similarly, it may be concluded that a similar state occurred in cases E.K. and J.T. by damage in the vicinity of the anteromedial thalamus bilaterally.

Such an implication of the importance of the antero-medial thalamus would not deny but rather emphasize the symptomatology produced by hypothalamic lesions in view of the intimate relation of this region with the hypo-thalamus by way of the mammillo-thalamic tract and the periventricular fibre system (Clark, 1932; Papez, 1937; Walker, 1938; Alpers, 1940; Ingram, 1940), and would be in agreement with the important postulates of Penfield and Jasper (1947) concerning the location of the "highest level", Papez (1937) concerning the relation of the hypothalamus, anterior thalamic nuclei, the gyrus cinguli and the hippo-campus to emotional dynamics, consciousness and related functions, and Cairns, Oldfield, Pennybacker and Whitteridge (1941) concerning the relation of a hypothalamic-thalamic system and its cortical connections with the synthesis of impressions from the outside world with those from the interior of the body, a synthesis on which consciousness may depend.

In the case of J.B. following the intracranial extension of a parotid gland tumour into the region of the floor of the third ventricle, this patient demonstrated the gradual onset of progressive loss of memory, drowsiness and confusion (a syndrome best termed "amentia") and impairment of speech.

This lesion was manifestly a unilateral destruction of the left mammillary region of the hypothalamus, left midline nuclei and left dorsomedial nucleus of the thalamus.

It seems well established that lesions of the thalamus can give rise to personality disorders and evidences of an organic psychosis (Smyth and Stern, 1938; Stern, 1939; Stern and Dancey, 1942). There is also clinical and experimental evidence that hypothalamic lesions may give rise to similar symptoms (Fulton and Ingraham, 1929; Alpers, 1940). In this case it is impossible to conclude whether the hypothalamic or thalamic lesion was predominantly responsible for these changes. But the absence of other hypothalamic symptoms, such as loss of temperature control, obesity, diabetes insipidus and hyperphagia, tends to incriminate the thalamus. Furthermore, the symptomatology is strikingly similar to the case of progressive drowsiness, confusion and dementia associated with a glioma of the massa intermedia described by Smyth and Stern (1938).

The component of drowsiness in J.B. may be accounted for by the hypothalamic damage or by damage to the mammillo-thalamic and periventricular fibre system and the nuclei of the midline.

In both the case of J.B. and E.K. an essentially unilateral lesion must have been responsible for the production of symptoms. If the hypothalamic injury was responsible it would not be in exact accord with the experimental findings of Ranson in lower animals (Ranson, 1937, 1939), whose evidence indicated that a bilateral lesion was necessary to produce hypersomnolence.

The impairment of speech in Case J.B., without dysarthria, cannot be classified under the present concept of aphasia. The speech difficulty seems to have arisen simultaneously and progressed with the degree of amentia, which suggests that the speech difficulty was a manifestation of the general state of mental deterioration. He could utter simple words and answer elementary questions but any attempt at speech involving any complex neural processes was not forthcoming.

Mutism occurred in the three other cases of thalamic damage (G.K., E.K. and J.T.) and it may well be that the speech impairment in this case is a milder degree of the same mechanism.

2. Electroencephalographic changes with replacement of normal rhythms by very low voltage slow waves.

This remarkable replacement of normal cortical rhythm by delta waves between one and five per second occurred in cases G.K., E.K. and J.T. Electroencephalographic study was not made in the case of J.B.

Such replacement of normal cortical rhythms by delta activity has been described before in lesions of the diencephalon (Walter, Griffith and Nevin, 1939; Cairns, Oldfield, Pennybacker and Whitteridge, 1941; Cobb, 1945).

In the light of recent experimental work demonstrating the influence of the anteromedial thalamus on the entire cortical rhythm in lower animals (Morison and Dempsey, 1943; Jasper and Fortuyn, 1947) it seems possible that these slow waves represent the cortical imprint of thalamic injury in this region. The fact that stimulation of the injured right thalamus in the case of G.K. produced three per second slow waves conducted to both frontal regions would tend to support such a theoretical concept. It is further possible that the decrease in seizures both electrographically and clinically in case G.K. following operative intervention in the third ventricle was due to either temporary alteration of pathways essential for the conduction of the abnormal discharge or to some "central pacemaker" initiating the abnormal rhythm.

B. DIENCEPHALIC ABLATIONS IN ANIMALS

The three control animals show that the anaesthesia, the attachment of the dural screw electrodes, the implantation of the electrodes within the diencephalon and the stimulation carried out for control of placement do not cause either electroencephalographic abnormality or change in behaviour following operation.

Furthermore, comparison of the anatomical lesions in the group showing marked behavioural or electroencephalographic change with those in the group showing little or no change following operation demonstrate that such changes are not dependent either on the size of the lesion or on diffuse oedematous and vascular changes, but rather are dependent on precise anatomical localization of the lesion.

Akinetic, apathetic state with thalamic lesions

Of the group of 9 cats with lesions in the region of the anterior nuclear group of the thalamus and upper end of the mammillo-thalamic tract 8 showed a markedly akinetic state and one other animal P8 379, although quiet following the operation, did not show the same degree of change as the other animals in this group. Comparison of the lesions histologically showed that in cat P8 379 there was less involvement of the mammillo-thalamic tract than in the other animals and it was concluded that the behavioural changes were more

dependent on damage to this tract and to neighbouring fibre systems than upon the damage to the anterior thalamic nuclei themselves.

Only 3 cats in this group could be classified as hypersomnolent (cats P8 229, P8 352, P8 353) and this state was transitory occurring only on the first postoperative day. These animals on the second postoperative day showed the same behaviour as the others in this group. For the most part the animals were not asleep but remained crouched without spontaneous movement with their eyes open and following movements about them. They did not feed themselves, and if they were not fed they lost weight and died. They did not groom their coats which became matted and filthy and they showed no interest whatsoever in their environment. This state continued to be most marked for the first ten to fourteen days when there was some improvement, and they began to feed themselves. However, there was a marked loss of initiative, of grooming, and of spontaneous movement which persisted for as long as the animal lived.

The fact that the reflexes and hopping and placing reactions were normal in these animals indicate that the akinetic state was not dependent upon paralysis of the cortico-spinal system.

The akinetic state appears from all the evidence at hand to arise from damage in the region of the upper end of the mammillo-thalamic tract and adjacent nuclear and fibre connections. This conclusion would be in agreement

with the views expressed by Ranson (1939) that somnolence arises when the emotional drive of the hypothalamus is eliminated, this drive being exerted upward on the thalamus and cerebral cortex, as well as downward through the brain-stem, spinal cord and peripheral nervous system.

Akinetic state and catalepsy with thalamic lesions

Both the cats with lesions in the midportion of the mammillo-thalamic tract and intralaminar nuclei showed catalepsy and loss of spontaneous activity.

Histological analysis of lesions in other animals which did not show catalepsy would tend to indicate that this group of symptoms is more dependent on damage to the midportion of the mammillo-thalamic tract and neighbouring fibre systems than in damage to the intralaminar nuclear group.

The similarity of the behaviour in these two animals to those described by Ingram, Barris and Ranson (1936) with lesions in the region of the mammillary bodies would seem to indicate that the mammillary bodies and the mammillo-thalamic tract are the specific areas injury to which gives rise to these symptoms.

Catalepsy and unconsciousness with lesions of mammillary bodies

In the two animals with bilateral lesions of the mammillary bodies both animals were found to be profoundly unconscious on the first postoperative day and could not be aroused. This

persisted for four days in one animal until it died. In the other animal the profound unconsciousness was replaced by catalepsy on the second postoperative day.

In one animal with a unilateral lesion confined to the right mammillary body and mammillo-thalamic tract catalepsy was marked.

Such evidence would suggest that not only may catalepsy arise from damage to the mammillary bodies and mammillo-thalamic tract but also that such symptoms may arise with a localised unilateral lesion in this region. It would also seem that the mammillary bodies and mammillo-thalamic tract play an important part in the mechanisms of consciousness and sleep in the cat.

Although no anatomical studies have been made in Monkey P8 412, the lesion is estimated to be in the region of the midportion of the mammillo-thalamic tract. Following this lesion there was a marked change in the animal's behaviour. The animal became docile and stolid, and lost emotional expression of the face. Although quiet, the animal has never been unconscious or hypersomnolent although it has appeared drowsy at times.

Electroencephalographic changes

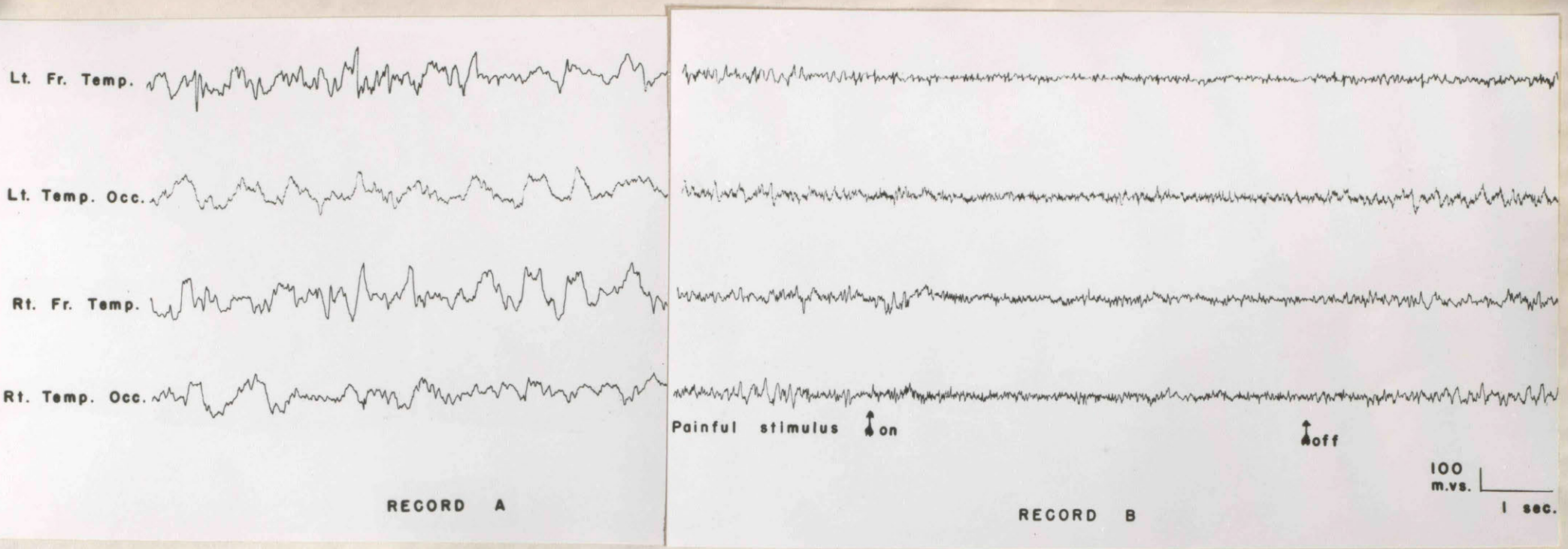
Most marked electroencephalographic changes were seen in the 9 animals with lesions in the region of the upper end of the mammillo-thalamic tract and anterior nuclei of the thalamus. This change consisted of a generalised slowing of cortical activity similar to that sometimes seen in the

normal, unanaesthetised sleeping cat; the animals were not asleep however. When these animals were stimulated there was some return of alpha rhythm but there was never the same degree of general cortical excitation as was seen when a normal sleeping cat was stimulated (Figs. 37 and 38). Furthermore, random slow activity between one and four cycles per second appeared regularly in the nembutalised record directly following the ablation.

In the studies with cats no conclusive abnormality could be discerned following ablation of the inferior portion of the mammillo-thalamic tract and the mammillary bodies although slow activity was occasionally seen.

In monkey P8 412, however, following a lesion estimated to be in the midportion of the mammillo-thalamic tract, the postoperative unanaesthetised record varied from normal alpha rhythm to delta activity depending on the state of the animal. Curiously, the alpha rhythm changed to delta activity with stimulation and the change persisted when the animal was struggling which is the reversal of the normal relation between alpha and delta activity with stimulation.

The electroencephalographic evidence would tend to suggest that there had been some interference with the sleep-wake mechanism following the lesions in the region of the mammillo-thalamic tract, an interference which was more marked when there was damage in the region of its thalamic terminations.



CORTICAL EXCITATORY STATE OF A NORMAL UNANAESTHETISED ANIMAL

Fig. 37

Record A shows the cortical activity obtained during relaxation with apparent sleep.

Record B shows the cortical activity in the same animal during the relaxed waking state when a painful stimulus is applied.

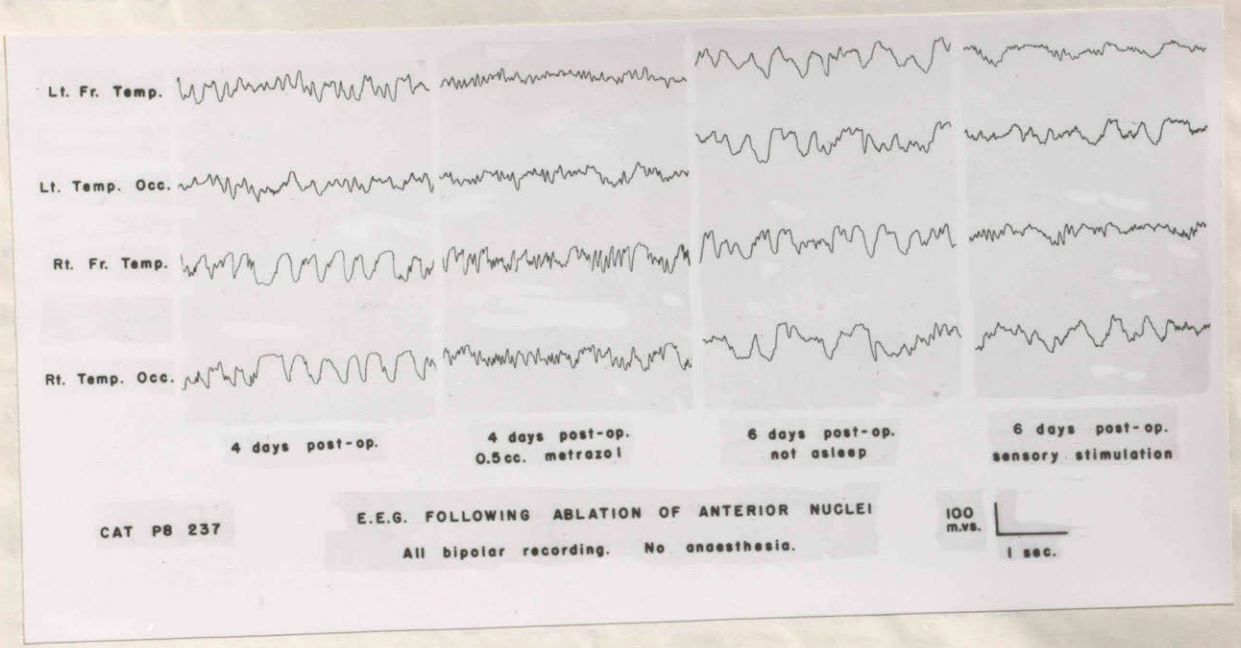

Lt. Fr. Temp.
Lt. Temp. Occ.
Rt. Fr. Temp.
Rt. Temp. Occ.
4 days post-op.
4 days post-op.
0.5cc. metrazol
6 days post-op.
not asleep
6 days post-op.
sensory stimulation
CAT P8 237
E.E.G. FOLLOWING ABLATION OF ANTERIOR NUCLEI
All bipolar recording. No anaesthesia.
100 m.vs.
1 sec.

Figure 38

Autonomic changes

It was noted that lesions in the region of the midportion and upper mammillo-thalamic tract were almost invariably accompanied by a persistent tachycardia, by a temporary but nevertheless severe hyperthermia, and by pilo-erection most marked along the trunk and back.

Lesions in the mammillary area give rise to bradycardia and loss of temperature control varying from hypothermia to hyperthermia.

Miscellaneous observations

It was noted that lesions of the dorsomedial nucleus gave rise to an absence of response to painful stimuli.

In one animal with a bilateral lesion in the anterior nuclear group of the thalamus there was a superficial erosion of the gastric mucosa. Since this remains an isolated finding its relation to the lesion must remain undetermined at the present time.

One animal with a bilateral lesion involving the lateral thalamic nuclei showed an abnormally reactive response to painful stimuli, a response which had not occurred prior to operation, and which persisted for three weeks until it was sacrificed.

VII. SUMMARY

Pathological study of four cases of diencephalic damage in man reveal that a state of akinetic mutism and impairment of consciousness associated with marked electroencephalographic abnormality may arise following damage to the anteromedial thalamus, and that a state of progressive loss of memory, drowsiness, confusion and impairment of speech may arise following unilateral damage in the mammillary region of the hypothalamus and in the region of the midline and dorsomedial nuclei of the thalamus.

This evidence would seem to substantiate the hypothesis that the activity of certain regions of the brain is more closely related to the existence of consciousness than others, and that mechanisms essential to consciousness exist in the anteromedial thalamus, in the mammillary region of the hypothalamus and in related fibre systems. Furthermore, electroencephalographic study indicates that damage to these mechanisms essential to consciousness is accompanied by generalised slowing of cortical activity showing similarities to records obtained during deep sleep in the normal subject.

Experimental studies in animals reveal that akinetic and apathetic states may be obtained with lesions in the region of the anteromedial thalamus and that these states are associated with electroencephalographic abnormality showing many similarities to records obtained during sleep.

Stimulation, however, never produces the same degree of cortical excitation in these experimental animals as in the normal animal.

Akinetic and cataleptic states were produced in animals with thalamic lesions in the region of the mid-portion of the mammillo-thalamic tract, and cataleptic and unconscious states were obtained by both unilateral and bilateral lesions in the region of the mammillary bodies and inferior portion of the mammillo-thalamic tract. Electroencephalographic changes were not marked in this group.

The evidence from studies in experimental animals suggests that the region of the mammillo-thalamic tract and immediately adjacent structures play an important part in consciousness and the sleep mechanism in animals.

Conclusions

Mechanisms essential to consciousness in man exist in the region of the anteromedial thalamus and in related fibre systems. Damage to these mechanisms may result in akinetic mutism and impaired consciousness associated with electroencephalographic abnormality.

Ablation studies of the diencephalon in animals suggest that the region of the mammillo-thalamic tract and immediately adjacent structures (from the mammillary bodies below to the anterior nuclei of the thalamus above)

play an important part in consciousness and in the sleep mechanism of cats.

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