EXPERIMENTAL EPILEPSY

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A THESIS PRESENTED TO

THE FACULTY OF THE GRADUATE SCHOOL OF ARTS AND SCIENCE

OF MCGILL UNIVERSITY

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE.

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From the Department of Neurosurgery.

EXPERIMENTAL EPILEPSY. A STUDY OF THE EFFECTS OF CEREBRAL WOUNDS AND CEREBRAL EXCISIONS. WITH A REVIEW OF THE LITERATURE OF POST-TRAUMATIC EPILEPSY.

by

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INTRODUCTION.

That convulsive seizures may follow injuries to the head was probably known by pre-historic man. Nevertheless, despite the age-old recognition of the relationship between head trauma and certain forms of epilepsy, and despite the untold investigations into the treatment of this unfortunate sequela, amazingly little progress has been made in an understanding of the underlying cause and the basic principles of therapy.

Adapting the definition of Lennox and Cobb (1928) as applied to the entire field of convulsive seizures, we may limit ourselves to a discussion of "a syndrome characterized by the sudden appearance of paroxysms, of which convulsive movements or loss of consciousness or both, are a principal element", but which, in the class of convulsions under discussion are associated with definite and demonstrable injury of the brain and its envelopes, due to violence.

The work herein reported comprises an integral portion of an experimental attack upon the problems presented by post-traumatic epilepsy which is being carried on in the Department of Neurosurgery. Briefly the thesis underlying the attack is as follows: 1. Nervous control of the vascular supply to the brain must be regarded as an experimentally proven fact (Cobb and his group 1928-1930, Hassin 1929). 2. The vasomotor mechanism of the epileptic seizure as discussed by Hughlings-Jackson and elaborated by A.E. Russel (1909) and others becomes

therefore, a physiologic possibility through nervous reflex. 3. A contracting cerebral cicatrix, by pulling upon the vasomotor nerves incorporated in the scar could, theoretically, initiate a nervous reflex which, by causing a vasomotor change would in turn initiate an epileptic seizure. Some authors advance the theory that the vasomotor change gives rise to cerebral anaemia which is considered to be responsible for the seizure. If the anaemia were local the resulting convulsion would in all probability be local; if it spread slowly Jacksonian epilepsy might result, while if the anaemia rapidly became generalized a full convulsive seizure might take place.

There is as yet, however, no unanimity of evidence as to what the change subsequent to vasomotor activity may be.

If, then, the cerebral cicatrix may justly be regarded as the immediate cause of the epileptic seizure, the surgically clean removal of the scar should prevent further attacks if removed at an early enough date in the course of the convulsions.

The experimental attack readily suggests itself. It was planned to take a series of animals, establish in the individual animal the minimum convulsant dose of one of the standard convulsant drugs. Thereafter wounding of the cerebral substance was planned for one group with the expectation that the convulsant dose would be lowered. In another group surgically clean removal of blocks of cerebral tissue was to be attempted, with

establishment thereafter of the post-operative convulsant dose. It was hoped that it might be possible by comparison of the post-operative doses of the two groups, and by a study of the structural histology to establish a significant difference between the groups. Later, after determination of the post-operative threshold in the wound animals, excisions of the scarred area were to be done with subsequent redetermination of the minimum convulsant dose.

A further suggested field of study, but one which cannot concern us in this paper, is the question of the presence of vasomotor nerve fibers upon the cerebral vessels themselves, as distinct from the pial vessels. Then for therapeutic reasons the sources of any fibers to the cerebral vessels, pial or deep cerebral, require determination. Finally the presence of vasoconstrictor fibers in the scar itself, or in the meningo-cerebral cicatrix, stands as a necessary support to the completeness of the study. All of these latter questions must await another report from the Department.

Early Historical References.

In the Broca Museum in Paris are trephined skulls of neolithic man which Broca argued as evidence of fanciful, ritualistic or religious procedures, ~~and~~ Victor Horsley agreed ~~argued~~ that the trepanations were in some instances attempts to cure Jacksonian convulsions (Ballance 1922). These may well have been traumatic in origin. Hippocrates pointed out that a blow on one side of the head might be followed by contra-lateral paralysis or convulsions. The evidence that he trephined for such conditions seems not to be definite. Likewise, although Celsus and Galen both used the trephine, that they did so for the treatment of post-traumatic epilepsy is doubtful. References to trepanation for abscess and for fracture of the skull are frequent in the writings of the thirteenth, sixteenth and seventeenth centuries. Percival Pott (1713-1788) indicates clearly that the symptoms following head injury are due to brain injury, not to the fracture of the skull. Jean Louis Petit (1674-1750) lists as indications for trephining: fracture, unconsciousness, hemorrhage from the nose, mouth and ears, paralysis and convulsions, and he states that trephining should not be done to cure convulsions but to remove the particular cause of them.

Ballance quotes a detailed statement of Peter de Marchettis of a case reported in 1665 (Medico-Cirugicarum, Obs: vii, p.11). "I remember having a consultation with the famous D. Julio Sala, professor at Pavia, about a man who had been wounded in the head with a dagger. Not only was the bone injured, but the membranes and even the brain. The external wound had been treated by certain practitioners and a cicatrix had formed. After two or three months

the patient was troubled with epilepsy and had a fit twice or three times a month. When asked by Professor Sala whether he had ever had an injury to the head, he replied that he had and pointed out the place. I immediately inserted a probe beneath the crust and found a penetrating wound and proceeded at once to operation and the opening of the parts. The next day I applied the trephine; yellow pus escaped. For twenty days I applied over the brain black western balsam with the use of which the wound granulated, and in thirty days the patient was cured of his wound and of his epilepsy." Such a clear description of a head injury followed by convulsions requires no comment.

Writing in the next century Astley Cooper in his Lectures on the Principles and Practice of Surgery relates a cure of Jacksonian epilepsy by the operative removal of a spicule of bone. The epilepsy began six months after the injury. Because of increase in the number of attacks decompression operation was done in 1822 - seventeen years later the man was still attack free (Cutter 1930). George James Guthrie (1785-1856) British surgeon in the Peninsular War, recognized that "local pain and epilepsy may follow fracture of the inner table and require operation" (Ballance). Larrey (1766-1842), Napoleon's surgeon general, makes frequent mention of traumatic epilepsy and relates one case of cure (Cutter).

Wells, writing in 1812 (Cutter), clearly describes the case of a negro who sustained a right parietal depression, subsequently had fits and hemiplegia. Trephining resulted in practical disappearance of the hemiplegia but the patient was still liable to convulsive seizures when excited. Benjamin W. Dudley, professor of Surgery in the Transylvania Medical School at Lexington, was the first American surgeon to give special attention to traumatic epilepsy and its cure by decompressive operation. Between 1818 and 1827 he reported five cases. All of these cases had too short follow-up periods for any significance to be attached to the results.

Bright (1836) deserves mention here because his is the first clear description of "Jacksonian" epilepsy - although not due to trauma but rather to a vascular accident.

John S. Billings, the founder of the Surgeon General's Library at Washington, in his first published medical article (1861) wrote on "The Surgical Treatment of Epilepsy" (Cutter). He lists seventy-two cases of decompression with sixteen fatalities, forty-two reported cures, four cases unimproved, the remaining ten were classed as improved although not entirely relieved. At least some of these cases were of traumatic epilepsy for he includes Dudley's cases.

It is with the pioneer work of Fritsch and Hitzig (1870), marking out certain centers of the brain by electrical stimulation, and by the more exact work of David Ferrier (1881) using the same methods, that the modern period of study of cerebral physiology was introduced. With the many studies during the earlier years of the nineteenth century of the problems of convulsions were now combined the results of modern physiologic methods. Leonard Hill, Victor Horsley, Hughlings-Jackson were among the many leaders who lent their energies to

the study of convulsive seizures. With the passing of time more and more of the problem was unfolded, with the results to be seen below.

The Centers Involved in the Epileptic Seizure.

The experimental evidence accumulated in the last century and the first decade of the present one concerning the centers involved in epileptic seizures was well summarized by Luciani (Human Physiology 1915). It was his conviction that direct or indirect stimulation of the motor cortex is responsible for the epileptic seizure and that the excitation of the bulb is a not indispensable factor, probably serving in only an accessory, complementary fashion.

Experimental work reported since the publication of Luciani's Physiology has required a recasting of conceptions. Briefly stated the evidence now at hand indicates that ablation of the motor cortex results in a raising of the threshold for convulsions, whereas minor wounds cause an irritative process with a lowering of the threshold. The latter fact has been well known for a century as will be detailed below.

In ablation experiments Pike and Elsberg (1925) determined a number of pertinent facts. They found that both tonic and clonic convulsions follow the administration of absinthe subsequent to the removal of one or both motor areas, "if an interval of time sufficient for return of good locomotor function is allowed to elapse after the experimental operation.. When only one motor area has been destroyed, there may be more tonic extensor spasm on the side which has been deprived of cortical influences, and slight extensor rigidity may be noticed for a short period after the convulsive phenomena have ceased. The greater susceptibility of the uninjured area is shown by the rolling of the animal to the side of the uninjured hemisphere during the absinthe convulsions".

Dandy (1927), failing to heed the warning of Pike and Elsberg and apparently unmindful of his criticism of Cobb's acute experiments with thujone (Dandy and Elman 1925), performed stimulation experiments immediately after bilateral ablation of the motor cortex. He found that convulsions could not be produced no matter what part was stimulated nor what strength of electrical current was used. He concluded that clonic convulsions without the participation of the motor cortex are impossible.

Sparks (1927) found that the removal of one motor cortex raises the minimum convulsant dose of thujone although clonic movements persist bilaterally.

Muncie and Schneider (1928) removed large portions of the cerebral motor cortex from one or both sides and found that the minimal convulsive dose of oil of wormwood for their animals (cats) was thereafter one and a half times greater than formerly. The convulsions were bilateral even after removal of the entire motor cortex of one side. There was observed, however, a weakness of the contralateral side. No spontaneous convulsions were observed in any of the operated animals, eleven in all, over a period of several weeks. That extensive cortical ablations cause a "hyposensitivity" to convulsive agents in contrast to the "hypersensitivity" caused by cerebral injuries, even minor ones, was first clearly indicated by Muncie and Schneider. The observation is an important one and deserves further confirmation and extension.

Dandy and Elman (1925) summarize the work of a long list of investigators who have produced convulsions by central nervous system injury. Brown-Sequard (1851) traumatized various parts of the neural axis and found that "lesions of the medulla, the cerebral peduncles, the corpora quadrigemina, or even injury to the sciatic nerves, were sufficient to cause convulsions". Westphal (1871) produced convulsions in rabbits by gently strikig their heads. Luciani (1878) found that spontaneous convulsions followed extirpation of the motor cortex, beginning on the side contralateral to the cerebral defect. A latent period varying from three days to eighteen months was required for the appearance of the convulsions, a monkey developed symptoms in three days. The attacks among the animals became more frequent and more severe and only two of fifty cats and dogs escaped death in status epilepticus. Goltz (1892) performed extensive extirpation experiments which resulted in the development of convulsive states. His dogs generally died in status epilepticus within an interval of a few months. The extirpations were not limited to the motor area but involved the occipital and temporal lobes as well. Laborde (1895) produced spontaneous convulsions in two frogs - in one after removal of a large part of the fore-brain, in the second after a needle prick of the corpora restiforma.

Sauerbruch (1913) using cocaine as a convulsant, found that monkeys and rabbits are much more susceptible to convulsions after injury to the left motor cortex, only one-fifth of the convulsant dose being required.

Syz (1923) cites the work of Barbour and Abel who found that fatigue, cold and subminimal doses of acid fuschin produced convulsions in frogs following brain injury, often of a trivial nature such as a simple brain prick. Syz himself concludes that injury to the brain, even as minor as a prick, causes increased absorption of convulsant dye.

Cobb (1922) found that two to three times the normal dose of thujone was required to produce convulsions in decerebrate animals. These were acute experiments.

Dandy and Elman (1925) performed simple extirpations of the cortex or subcortex over the Rolandic area, the occipital lobe and the cerebellum. In some cases a simple incision was made in the brain substance; in other areas a small foreign body was imbedded. Absinthe was given four to twenty weeks after the operations. Only one-third to one-seventh of the dose of convulsant drug was required post-operatively. "The experiments show conclusively that injury to the cerebellar and occipital lobes is far less effective in making the animal susceptible to convulsions, than is injury to the motor cortex. They also suggest that less absinthe is required to induce convulsions in occipital and cerebellar injuries than in the normal, but..... we are not willing, with the limited evidence at hand, to draw a positive conclusion in these cases."

Muncie and Schneider (1928) found that minute injury to the motor cortex of cats resulted, after several weeks, in the development of a hypersensitivity to wormwood oil, only half the previous dose

being required to produce convulsions. Injuries to the spinal cord had a similar effect. The cerebral injuries consisted of small puncture wounds in the motor area of three animals, none of which developed spontaneous convulsions. In these animals the prodromal signs were less marked, the convulsions were not so severe, and the exhaustion was not so great following the attack as in normal animals. In the animals deprived of extensive areas of cortex, and in whom larger doses (approximately half again) of convulsant drug was required, the prodromal signs were more striking, the convulsions were more severe and the exhaustion more extreme than in controls.

The Tonic and Clonic Elements of Seizures.

Many authors have felt that the cortex is responsible for the clonic phase of convulsions. "There was a complete absence of the tonic phase of the convulsions when the animal was kept under light ether anaesthesia. This was probably due to a lowered irritability of the cortical or subcortical mechanisms which are responsible for this phase." (Muncie and Schneider 1928).

Martin (1926) argues that the tonic stage was shown by Cobb (1924) with electromyograms, to be a tetanic state rather than one of increased tone. Though fits with the tonic element can be produced by cortical stimulation, similar fits occur in infants with unmyelinated pyramidal tracts, and therefore with a presumably functionless motor cortex. In his opinion there is nothing to suggest that the adult fit is any different from that of the infant. The clonic phase presents alternate motions of the lower limbs similar to spinal reflexes, of the upper limbs similar to those seen in quadriplegics only when cortical control is removed, of the face and jaw as seen in decerebrate animals. While all of these movements can be produced by cortical stimulation, he feels that is it unnecessary to invoke cortical activity in explanation of them.

Wyematsu and Cobb (1922) concluded that:

(1) Convulsions can be discharged from any part of the neural axis.
(2) Much smaller doses of convulsant drug (wormwood oil) are required for normal animals than for spinal preparations.
(3) After decortication, decerebration and spinal cord section the clonic movements are of slower tempo. In the latter case they are rapid above and slow below the cord lesion.

Lennox and Cobb (1928) conclude, "Fits can be set off by stimulation, or by disturbances such as anaemia, of various parts of the central nervous system, and convulsions may occur after removal of the cortex and even in the isolated cord. Thus one must return to the more general conceptions of etiology and consider focal lesions as the cause only when it is obviously indicated by the symptomatology and pathology".

Pike et al (1929) arrive at a conclusion similar to that of Lennox and Cobb, that under varying circumstances convulsions may be released from various levels. They adduce support for their argument from study of the convulsions of animals of lower phylogeny. Numerous other observers, Uyematsu and Cobb (1922) and Pollock (1923) among them, have reported experimental convulsions originating at various brain and cord levels.

A striking new conception of paroxysmal seizures, involving the autonomic centers, was suggested by Penfield (1929) after observation of a clinical case of recurrent waves of sympathetic disturbance caused by a tumor lying in the diencephalon - "diencephalic autonomic epilepsy". It provides another example that paroxysmal disturbances may arise from many of the nuclear masses of the brain other than those of the cortex.

So to Hughlings-Jackson's amazingly advanced views (1883) of three kinds of convulsions "true epileptic", epileptiform, and pontine and medullary, must be added recognition of still other convulsive levels.

The importance of bearing in mind the above conclusion lies chiefly in the value of a broad conception of traumatic epilepsy. It is unlikely indeed that the entire story is told when the dura is turned back and the surface of the cortex exposed. The presence of a normal appearing cortex does not at all rule out the possibility of a deep-lying cicatrix. Nor would it seem necessary to assume that when an area of scar is removed epileptic seizures need necessarily cease, or even be lessened in frequency or severity. It is too easy to think loosely and to forget that the cortical scar may be only one of the discharging areas in a brain whose physiology is disturbed. This warning must be borne in mind particularly in long standing cases, those which "have acquired the epileptic habit", whatever that term may mean. In the present discussion, however, we are concerned only with the more obvious cicatrices presenting at the surface of the brain.

REVIEW OF THE LITERATURE OF POST-TRAUMATIC EPILEPSY.

A review of the literature of this subject is fraught with great difficulty. In the first place there is not general unanimity of opinion as to the definition of traumatic epilepsy. Secondly, there is not agreement among the various authors concerning the division of cases into generalized and Jacksonian types, and the relative importance of trauma in the production of both. Thirdly, the figures of incidence vary from three to around sixty per cent, an indication of the unreliability of the gathered statistics. Fourthly, because of the etiology of the disease is so obscure the therapeutic attempts have been legion, and throughout a good deal of the literature the therapeutic results have been grouped regardless of the pathology found at operation and of the operative attack employed. Finally, and herein lies the crux of all attempts to arrive at an adequate judgment of any therapeutic attack studied from the clinical point of view, the study of the individual case is of greater value than the mass study of a series. The possible permutations of the various factors involved are too numerous for application of group study. Putnam (1901) indicated this when he wrote, "Such compilations have, to be sure, only a limited statistical value, since the grounds for valid classification and comparison of different cases are very imperfect. The study of the individual case is really of greater value."

In the Introduction we defined traumatic epilepsy for the purposes of this paper as, "a syndrome characterized by the sudden appearance of paroxysms, of which convulsive movements or loss of consciousness or both are associated with definite and demonstrable injury to the brain and its envelopes." As an all inclusive definition then those cases of seizures, almost always of focal type, occurring shortly after brain injury and before scar formation has occurred, should be included. It is our intention, however, to separate this group sharply and to drop it from consideration since its mechanism seems, at least superficially, to be of a somewhat different nature. The exact time at which intracranial scarring may be considered to become responsible for traumatic epilepsy is uncertain. It has become a definite possibility three months following the more severe head injuries. The time at which scarring may no longer be considered of importance is still more uncertain and undoubtedly varies with individual cases. Foerster and Penfield (1930) quote a case with onset of seizures fourteen years after injury, in which there was well marked scarring demonstrated histologically in the specimen obtained at operation. It seems reasonable that scarring might be held responsible over a much longer period of time.

There is almost general acceptance of the view that both generalized and Jacksonian seizures may follow after head trauma. Further there is evidence to show that those cases which had focal seizures immediately after injury, in contrast to those which developed them after three months or more, are rather more prone to the development of "spätepilepsie."

All the above points have been emphasized for at least one author, Turner (1927), has a quite different conception of the term. "By traumatic epilepsy is meant a disability characterized by seizures having the features of ordinary generalized epilepsy, occurring as a late phenomenon in consequence of a wound or injury to the skull or brain. The outstanding feature of this condition is the development of the disease after a latent period of several months, sometimes up to two or three years, following the trauma, and the absence of any definite or constant relation between the injured region of the brain and the method of onset of the fit. The fits resemble those of ordinary epilepsy and all varieties may be observed from a momentary "absence", lapse or vertigo, to the fully developed major seizure. The disability runs a chronic course and in the majority of cases some degree of mental enfeeblement tends to supervene. This disability is entirely distinct from focal or Jacksonian epilepsy following head trauma. The latter condition is not epilepsy in the proper acceptation of the term, rather it is a state of localized cortical irritation. It is observed within a short time of the infliction of the trauma; it is more amenable to surgical interference; it shows a tendency afterwards towards spontaneous cure, and once the attacks have ceased there does not seem to be any special tendency to relapse, or the development of traumatic epilepsy."

Lenormant (1921) points out that some macroscopic lesion is nearly always present in traumatic epilepsy. In twenty cases of his own he invariably found gross pathology. He cites two hundred and sixty-seven cases gathered by Tilmann of which two hundred and thiry-two showed gross lesions, and two hundred and forty-six of Braun of which two hundred and thirteen showed macroscopic findings. Lenormant believes that the findings in war injury would show a still larger percentage of gross lesions. He divides the findings at operation into: (1)Lesions of the bone, including thickening and condensation, exostoses, loss of cranial substance and closed fractures without external evidence. (2) Lesions of the meninges: thickening, cicatrization, cyst formation and oedema of the arachnoid, this last condition found by Tilmann in six of twenty cases and noted by Krause as well. (3) Cerebral lesions: cicatrization with or without inclusion of foreign body, superficial cysts the result of old superficial haemorrhage or areas of softening, deep cysts resulting from extensive cerebral destruction, haemorrhagic zones, areas of softening and abscesses.

To these various lesions it is difficult to ascribe their proper degree of importance. All must, however, act through the cerebral substance or through the cerebral circulation. Of the cerebral lesions themselves the depth and extent per se appears to bear no direct relationship to the ensuing convulsions (Lenormant). Behague (1919) feels that the nature and character

of the wound and the origin of the projectile are only of importance in the amount of damage caused. Clarke (1924) examined twenty-one cases with seizure, post-mortem. In two cases he found injury to the membranes only, in eight cases he found injury to the membranes and cortex, in eleven cases he found injury to the meninges and to the deeper parts of the brain. Gordon (1925) in thirty-three cases found eleven fractures of the skull with severe fronto-parietal haemorrhage, nine cases with pressure over the parieto-occipital region, five cerebral cicatrices and eight meningeal adhesions associated with frontal lobe cicatrices - all of these cases being drawn from civilian practice.

Incidence.

Peace Time Literature: Lenormant (1921) gathered together the reports of several authors upon the occurrence of traumatic epilepsy in times of peace. Brun, among two hundred and twenty-one cranial injuries of all types, reported eighteen cases - 8%. Braun in a similar group made up of two hundred and ninety-one cases, reported fifteen epileptics - 5.2%. Of these, there were thirty gunshot wounds one of whom developed epilepsy. Gordon and Wilson record fourteen epileptics among five hundred and thirty fractures of the base - 2.6%. Neumann, among one hundred and eight cranial traumata on an infants' service, found three cases of epilepsy - about 3%. This finding is in agreement with that of Ford (1926) that two or three per cent of all epilepsies seen in children are related to birth injury.

Muskens (1928) in one thousand cases of head injury seen in private practice found only eight epileptics. Steinhal (1929) quotes Reichman as finding a .5% incidence among six hundred and three peace time injuries while he himself, among five hundred and thirty-one cases seen in his own private practice between 1907 and 1926, saw only one epileptic.

War Wounds: The incidence of epilepsy consequent to war wounds is far higher than that noted above during peace time. Allen (1906) notes that among one hundred and sixty-seven skull injuries of the American Civil War twenty-three, or 13.7%, were on the pension list because of epilepsy. Among five hundred and seventy-one cases of recovery from gunshot wounds of the skull in the Franco-Prussian War, as reported by von Bergmann for the German Army, twenty-five or 4.3% developed epilepsy. If to these cases of epilepsy there be added those with periodical attacks of dizziness, numbness, trembling, et cetera, the percentage is raised to 26.7%. In the Russo-Japanese War T. Eguchi found thirty-five cases among one thousand skull injuries, 3.5%, but two years later Holbeck succeeded in tracing sixty-five cases which he had treated in the same war. Of these nineteen, or 29.2%, had become epileptic (Lenormant). Of this same group only six were epileptics six months following their wounding.

In the World War abundant material was provided for the study of this question, yet the results are strikingly discordant.

Sargent and Holmes (1916), reporting on six hundred and ten cases only 15% of which had been followed for more than a year, found thirty-seven epileptics, 6%. Eight of these cases, however, had had only one seizure; in only eleven were convulsions frequent.

Behague (1919) in a comprehensive study of the cases in P. Marie's clinic, numbering three thousand, six hundred and twenty-three head injuries, found an incidence of 12.11% of epilepsy. Two-thirds of the cases were generalized, the remaining third were Jacksonian. Lenormant points out the striking fact that this was an increase from the 5% reported by P. Marie and Chatelin in 1916, and from the 8% reported by the same authors the year following.

Voss (1921) confirms the increase in incidence with the passage of time. Among one hundred cases which he studied in 1917 37% had developed epilepsy. In 1920 he was able to trace seventy-three of the original hundred; of these 61.7% were subject to seizures. While it would seem obvious that there must have been a concentration of severe cases in Voss' clinic, the increased indidence among members of the same group cannot but be striking.

Lenormant (1921) adds the following figures:

French:

Souques, 9 in 33, 18%

Chiray, 57 in 276, 20.8%

H. Claude, 24 in 247, 10%

Villaret, 53 in 256, 20.7%

Babinski, F. Netter, 34 in 150, 22.6%

Carrière, in a collection of one thousand wounded, 6%

Sollier, 15%.

Tuffier and Gullain, 676 in 6,664, 10.4%

Billet (Statistique de l'Autochir. 6) 26 in 167, 5%

Belgian:

Derache, 2 in 24, 8.3%

Janssen-Denot, more than 10%

American:

H. Neuhof, 3 in 175, 1.8%

English:

W.W. Wagstaffe, 9 in 710, 1.3% (See later figures below)

German:

Röper, 16 in 134, 11.9%

Tilman, 15-20%

Amelung, 74 in 520, 14.2%

To these figures should be added those of later studies. Rawlings (1922) among four hundred and fifty-two British cases found an incidence of 25% of seizures. These results were based upon a questionnaire sent out to seven hundred and fifty men.

The results cannot then be considered to be entirely reliable but are of significance because of the time elapsed since injury.

Turner (1923) in a review of eighteen thousand cases of gunshot wounds of the head among British troops found that only eight hundred, or 4.5% had become epileptic.

Falling between the percentages of Rawlings and Turner is that of Wagstaffe (1928). Of the British figures his can probably be regarded as the most significant both from thoroughness of study and duration of period of observation - eleven years or over. Of a total of three hundred and seventy-seven cases of all kinds, (penetrating dura, fractured skull but dura not penetrated, scalp wound only, concussion and fractured base) thirty-seven or 9.8% developed seizures. A marked increase from his previously given figure of 1.3%.

Schönbauer (1929) cites ninety-five cases of Bouskin, of gunshot wound of the head, thirty-two of which developed late epilepsy. He mentions also forty-three cases of Bychovsky reported in 1925. Of these sixteen or 37% were reputed to be suffering from Jacksonian attacks.

Steinhal (1929) mentions Brun's seven epileptics among twenty-one destructive lesions - 33.3%, and also Melzner's figures ranging between 12% and 40%. On the basis of the six hundred and thirty-nine surviving cases of gunshot wound studied so carefully by himself and Nagel two years previously, he arrives at a figure of 28.9%, one hundred and eighty-five cases of typical epilepsy. If von Bergmann's lead of including cases of dizziness et cetera is followed, the percentage is raised to 35.5%.

If, then, the last British figures, those of Wagstaffe, made up of three hundred and seventy-seven cases and those of Steinhal, six hundred and thirty-nine cases, are contrasted there appear great differences. The German incidence (28.9%) is three times that of the English (9.8%). Steinhal maintains that wounding of the dura plays little part whereas Wagstaffe finds epilepsy nearly ten times more common after penetrating wounds of the dura than after non-penetrating. These two glaring differences in result can only mean lack of a common basis for classification and understanding.

Relationship of Site of Wound to Occurrence of Epilepsy.

Concerning this question there is agreement among most, but not among all, of the authors. The concensus of opinion is that wounds of the parietal region are most apt to give rise to seizures. Buzzard (1916), without giving evidence, dissents from this view though he does state that the location of the injury may modify the features of the attack. Rosanoff (1925) likewise disagrees. He cites Borischpolsky's group of one hundred and eighty-five gunshot wounds of the head, ninety-two of which involved the parietal region with the occurrence of attacks in only seven or 7%, whereas in the remaining ninety-three cases attacks occurred in six, or 6.5%. Among nineteen cases of epilepsy from a group of two hundred and sixty-six studied by Holbeck, seven had wounds of the motor area 36.8%, twelve of other regions. This

high percentage is not in agreement with Borischpolsky's figure nor with Rosanoff's own findings. He, in the series of forty-five epileptics cited in his article, included thirty-five occipital injuries with only ten of other regions. On the other hand, in a second series forty-five in number, in which attacks were infrequent he included thirty-three wounds of the motor cortex. Eight of these were free of attacks for more than six years, six for more than five years, seven for more than three years, the others for a lesser period.

More in accord with the earlier findings of Holbeck given above are those of the following authors quoted by Lenormant. Eguchi among his thirty-nine cases of war epilepsy found the parietal region involved in twenty-five, 64%. F. Netter among thirty-two concussions found evidence of temporo-parietal involvement in twenty-seven, 84% - obviously a less reliable group upon which to base conclusions. Behague, among his cases, incriminated the parietal region in 55.2%, the frontal in 26.93%, the occipital in 10.53%, the temporal in 8.53%. Voss' figures correspond very closely; the parietal region 57%, the frontal 26%, the occipital 16%. Billet, in a small series of twenty-seven cases, found the parietal region wounded in 51.9%, the frontal in 25%, the occipital in 11%, the temporal in 7.4%.

Of the thirty-three cases of penetrating wounds of the dura having seizures which Wagstaffe reported, ten were situated in the parietal region, ten in the frontal, four in the fronto-parietal, four in the occipito-parietal, three in the occipital and two in the temporal.

Bouskin's cases, quoted by Schönbauer, ninety-five gunshot wounds of which thirty-two developed late epilepsy were divided as follows: 40% parietal, 30% temporal, 20% frontal, 3% occipital.

Steinhal's figures are not so high for the parietal region, 23.7%. Next he places wounds of the occipital zone 18%, to be followed by the frontal region, 14.6%, witn the temporal pole held responsible in 12.2% of cases.

Relationship of Site of Wound to Type of Seizure.

As might be expected most of the wounds of the parietal region are Jacksonian in type, while those of the other areas are more apt to be generalized. Lenormant quotes the following figures from Behague:

Region.	Percentage of Epilepsy.	Percentage of cases generalized.
Parietal.	14.21	31.0
Frontal.	11.06	85.84
Temporal.	8.02	72.72
Occipital.	7.75	70.00

Rawlings found that among the four hundred and fifty-two men answering his questionnaire, regardless of the site of their wounds, 57% suffered from epileptiform attacks, 23% from Jacksonian seizures, 16% had fainting spells, while 4.5% were grouped under "slight and uncertain". These figures are in approximate agreement with Behague's generalization, two-thirds of the cases generalized in character, one-third Jacksonian. Of the two types the Jacksonian is prone to appear a little earlier (Behague).

Wagstaffe feels that late epilepsy is much more common in those cases which show transient Jacksonian attacks within a few days of injury. These cases may, of course, become late epilepsy of either general or Jacksonian form.

Importance of Primary and Secondary Healing:

Schönbauer states that primary wound closure does not protect against epilepsy and objects to his quoted statement from Kaeger who cited forty cases of primary healing with three cases of late epilepsy (reported in 1920). Steinhal agrees that primary closure plays no part and gives as evidence:

Wounds involving the dura:

1. Operation within twenty-four hours
   Primary closure, 38 cases 14 epileptics 36.8%
   Healing later, 11 " 28.9%

2. Open handling, 111 " 37 " 33.3%
   (And of this group of thirty-seven, epilepsy persisted in twenty-eight, 25.2% of the one hundred and eleven cases.)

The Role of Infection:

Steinhal reports in his series studied in conjunction with Nagel the following figures:

67 cases complicated by infection, 32 epileptics, 47.7%
160 " non-infected, 50 " 31.2%

These figures are such as might be expected if one considers the degree of scarring as of some importance, for the gliosis occurring in infection must be more marked than in clean wound healing.

The Presence of Foreign Bodies:

Wagstaffe found that 36% of his cases with seizures carried within their heads a foreign body, whereas 25% of those free of attacks did likewise. This cannot be considered a significant difference. Steinhal asserts that deep lying fragments play no significant part and quotes Redlich's view in his support.

Mental Deterioration:

One gains a very definite impression in going over the literature that traumatic epilepsy carries with it nothing like the toll of mental disintegration that accompanies idiopathic epilepsy. Turner mentions loss of memory, lack of attention et cetera, signs common enough in cases after moderate skull fractures allowed freedom too early in convalescence, a finding therefore not peculiar to traumatic epilepsy. Voss (1921) mentions the occurrence of psychic changes, particularly the depression occurring not seldom after an attack. Wagstaffe mentions that of the five surviving cases of penetrating wounds of the dura in the frontal region all showed well marked mental deterioration. Steinhal reported that among two hundred and twenty-seven traumatic epileptics only eleven were lost to society, and only in seventeen was the character change marked. The occurrence of mental changes must be relatively infrequent, ~~however~~, if one may judge from the scant attention paid to the subject by the various reviewers.

The Importance of Accessory Factors in the Occurrence of Post-Traumatic Epilepsy and Theoretical Mechanism of the Attack.

The explanation of the discrepancy between the number of head injuries and the incidence of epilepsy, and of the fact that wounds of the severest type situated directly in the motor area may not give rise to seizures, has been sought by many.

Turner considers cerebral vasoconstriction occurring reflexly as the result of anchorage of the brain to the skull by adhesions as being the most probable explanation of the mechanism. The inconstancy of development of seizures among wounds he explains by assuming an inherited constitution predisposing to attacks, and explanation which he frankly admits he cannot support by the evidence available.

Behague suggests that the seizure is consequent to cerebral swelling resulting from irritation. The swelling causes further irritation and initiates an attack. Lues, alcohol, hysteria and tainted heredity may all contribute.

Lenormant agrees that lues and alcohol augment the epileptic tendency. Concerning heredity he only remarks that opinions differ and does not commit himself.

Schönbauer considers the epileptic attack to result from a combination of two factors, stimulation by the local condition and an increased excitability of the brain. Determination of the latter condition is variable. Acute and chronic infections are of importance. Pregnancy and labor may play a part. He wisely points out that the hereditary factor is a difficult one to judge for in some instances no amount of questioning can elicit information, at other times trifling familial affections cannot be properly evaluated.

Steinhal, in pursuing the reasons for the "epileptic tendency" suggests vasomotor instability as playing an important rôle; a view which is more and more gaining in popularity and which is coming to have a part in the explanation of idiopathic epilepsy as well (Lennox and Cobb). Steinhal conceives of traumatic epilepsy as resulting from an interaction of local irritation and constitutional vasomotor imbalance. He considers that in early epileptic seizures the local irritant is the more important factor, and that in late epilepsy the local irritant assumes less importance. This latter view is, however, hardly consistent with the histological evidence of mildly progressive cicatrizing activity presented in a ~~previous~~ following chapter.

Just what the relationship between the "epileptic habit" and vasomotor activity may be is a matter for speculation. Conceivably the repetition of a vasomotor reflex may make its initiation progressively easier. As yet there is no evidence available on this subject.

Leriche and Wertheimer (1925) on the basis of eighteen of their own cases conclude that post-traumatic Jacksonian epilepsy is always accompanied by a neuroglial scar, meningeal lesions being significant only in that they tend to interfere with the cerebro-spinal fluid circulation. They feel that a vasomotor activity, evidence for the support of which has been seen at many operating tables including their own, must be the variable factor, linked with the constantly active neuroglial scar. These authors attempt to control the vascular phenomena, which are at present outside the reach of the surgeon, by cerebro-spinal fluid pressure control, raising or lowering it as necessary.

Foerster (1925) in a comprehensive paper maintains that all epilepsies owe their origin to the elaboration of an irritative agent the result of the disease process and analagous to faradic, mechanical, chemical or thermal stimulation - any one of which may set off an attack. However, since epilepsy does not result in all persons possessed of the diseases capable of elaborating the irritative agent, there must be a second factor, a predisposition, a special state of hyperexcitability of the central nervous system, just as a peripheral reflex may be greatly exaggerated. This he believes to be due to an endocrine imbalance. Corpus luteum, persistent thymus and perhaps the pineal tend to greater susceptibility. The other glands, with the thyroid acting as a moderator, have the opposite action. That variations in the pH of the blood may also play an important rôle is indicated by the results obtained on hyperventilation and alkali injection. Also sensory disturbances of many kinds, pressure on peripheral nerves, phymosis, optic difficulties et cetera, may cause the flood to over-reach its banks, presumably in traumatic as well as in idiopathic cases.

Spontaneous Cures and the Conservative Treatment.

That some cases of traumatic epilepsy recover spontaneously is a common observation. Schönbauer records four improvements in twenty-five unoperated cases - 16%: 8% of the cases not traced being classed as not helped. Steinhal includes in his series of one hundred and eighty-five epileptics sixteen cases of spontaneous cure - 8.6%. Twelve of these were focal in character, four general, nine "early", seven "late" epilepsies. It is important to bear in mind that "early" epilepsy connotes cases which are generally due to direct irritation and which are seen early in the course of head injury. It does not include attacks presumably precipitated by scarring. On this basis only seven spontaneous cures occurred in the series - 3.8%. Spontaneously healed cases are apt to be an ill-defined group; there are few cases for which some sort of therapy has not been attempted. Moreover, "spontaneous healing" would seem to be a misnomer. Certainly the evidence is slight that those cases involving brain damage ever experience recession of the scarring process, per se, undoubtedly a stand-still may occur in some cases. The cessation of attacks must be due rather to a diminution in the Krampfbereitgeshaft of Foerster, and it would seem likely then that attacks might well be expected to recur in at least some of these cases of Steinhal's.

Operative Procedures and Results.

In 1901 Putnam wrote "....it may be stated, as a fact which would probably be generally admitted, that operations for the relief of focal epilepsy, whether these aim at the removal of local sources of irritation or of diseased areas involving the cortex, or of the removal of apparently normal cortex, are often unquestionably of great benefit although they have not accomplished nearly all that was hoped of them." The same might have been said to be true of the generalized form resulting from trauma and, moreover, these statements both hold to-day as certainly as when Putnam wrote.

The operations devised for the treatment of traumatic epilepsy may be divided into three groups depending upon the end in view: the correction of the local condition, the abolition of irritative factors or the control of the abnormal physiologic mechanism responsible for the attack. Consideration of the second group would take us too far afield. Empirically it has been found that the correction of the local condition is not always a surgical possibility, and that in some instances where it has seemingly been achieved the epilepsy has been little affected. Logically, then, those means which seek to control the abnormal mechanism should be utilized, providing that the possibility of the local lesion being progressively destructive is kept in mind. This is the ultimate therapeutic goal to be hoped for. At present too little is known to make progress certain in this direction. It was in the hope of casting some light on the pathologic physiology of traumatic epilepsy that the work, of which this paper is a small part, was undertaken.

In this discussion, then, we shall be concerned only with the surgical handling of the local condition, leaving out of the discussion such operative attacks as ligature of the carotids, resection of the cervical sympathetic supply to the brain, ligature of the superior longitudinal sinus, ablation of the suprarenal capsule, et cetera; procedures which have been utilized chiefly in the treatment of idiopathic epilepsy. Nor can the prophylactic treatment of head injuries be discussed here, important as that subject is.

Treatment of the local lesion can be divided into attempts to alleviate pathology of the bone, of the meninges or of the brain. That bony spicules, depressed fragments and bony exuberances may give rise to seizures is undoubted. Smoothing of the inner table is essential in such cases and probably is effective in most instances in which this is the only structural pathology present, although statistics on this subject are lacking.

Injuries involving the meninges may only give rise to an arachnitis or may result in adhesions between the pia-arachnoid and the dura. Steinhal reviews comprehensively the opinions of many authors and the following discussion is based on his search of the literature. Guelke and others believe the attachment of the brain to the skull to be the significant factor in initiating seizures. Their attacks center on attempts by plastic operation to prevent adhesions. Fat transplants have been warmly recommended by Lexer, Guelke and Rehn. Martin and Reich, however, found that the fat transplant becomes involved in the scar. Lexer,

denying incorporation of the fat into the scar tissue, attributed Reich's failures to general brain damage, which operative procedures are powerless to help. Drevermann, reporting the operative results obtained at Lexer's clinic, found that of eight war wounds two had been attack free, forty-one and sixty-three months respectively; one was improved and five showed no improvement. Results which justify, in Steinhal's opinion, the pessimistic view held by Lexer and others of the operative treatment of traumatic epilepsy. Fat transplants have even been used to fill great holes left after excision. Foerster believes that such transplants should be removed, Muskens deprecates their use and Steinhal himself thinks that they are certainly without beneficial effect. He is of the opinion that even free fascia becomes involved in scar tissue.

Strachauer (1919), following the lead of Kirschner who reported seven years earlier seventeen cases in which fat free fascia lata was used with cessation of convulsions, employed the method in eleven cases, two as a prophylactic measure. One of the eleven cases was not at all improved, the others were all greatly improved; the oldest was followed for only four years, however.

Burchart (1923) reported a case operated four years previously, and a fat graft being inserted into the dural defect. The seizures continued. Burchart removed the fat transplant, took normal dura from nearby and substituted it for the fat transplant. Subsequently he replaced the defect in normal dura with a fascial transplant. The case was thereafter attack free for two years and he conservatively suggests further trial of the method.

Steinhal mentions Bier's attempt to prevent adhesions by filling the operative defect with salt solution, thereby hoping to raise the edges of the defect sufficiently to keep them free. Block reported one improvement in six operations with this method and it would seem perfectly justifiable to question the part played by the salt solution in this one case. Finisterer felt that simple removal of the scarred dura, followed by replacement of the defect, should suffice to prevent adhesion of the brain to the skull.

Lenormant also discusses the handling of the dura at operation, citing a number of procedures, among them the following: Krause used and recommended Brünning's method of splitting the dura and folding it over like a leaf to close the defect. Hamant reported favorable results in two cases in which he placed a sheet of catgut between the skin and the dura. However, Gaudier and Billet each found in one case that the catgut was not tolerated, in one case it was removed at the end of two days, in the second at the end of twenty. Lenormant reviews the use of cartilage, hernial sacs of fascial, fat and peritoneal transplants, and concludes that almost invariably they become incorporated in the scar, become fibrous and are of no value in isolating the brain and meninges, nor in opposing the regrowth of the cicatrix. At best, he concludes, they are useless and often are harmful.

Excision of the epileptogenetic focus was first undertaken by Horsley in 1886 and since then the method has been used in both traumatic and idiopathic epilepsy when there has been an indication of a fairly definite center. Lenormant reports that the procedure has been severely criticized in France and discounts it on the basis that the lesions are usually too large to permit of removal. He found that Krause, Friedrich and Rasumowsky favored it. The latter two and Schulze-Berge all reported cases cured by cortical excisions, previously not benefited by other operations. Muskens has reported a case attack free for twelve years following excision of an irritable zone of cortex (since reported attack free for seventeen years). On the other hand, Tilmann in twenty cases and Frazier in twenty-seven cases of traumatic epilepsy never had occasion to use the procedure. Braun reported ten cases in which there was no definite evidence of brain pathology in which the operation was performed with only two favorable results and eight failures. A much more favorable result was obtained, however, in fourteen cases in which the cortical zone was manifestly altered. Among this group there were ten favorable results and only four failures. Krause (Sargent 1922) gave details of two cases with our visible lesion in which he excised the primary focus. One patient eight years later had only occasional twitchings, the second died shortly after operation in status epilepticus. He considers the resultant scar to be of no importance. Sargent in discussing gunshot wounds states that "... the results of such excisions

in patients suffering from focal fits without visible lesion has not proved very encouraging even in the hands of the most expert operators. Gordon (1925) makes, ~~however~~, the unsupported statement that "deeply seated traumatic cerebral cicatrices if removed, will only be substituted by surgical cicatrices with no results as far as the convulsive seizures are concerned."

Undoubtedly the best studied group of scar excision is that of Foerster. He has written at length conerning the theoretical reasons for his adoption of the procedure and his technique has become well-known even on this continent. In 1925 he reported the following post-traumatic cases, all excisions in the various areas as indicated. Frontal eye field, two cases, one attack free for three years, the second died at operation. Post-central, eight cases, two attack free for more than three years, four for more than two years, one for more than one year and one for a month and a half. Parietal adversive, four cases, one attack free for more than four years, one for one year, one for two months. The fourth was not improved, in this instance proper duraplasty was impossible. Occipital field, seven cases, one died post-operatively, one died a year after operation of an abscess, but had been attack free for that year, two were attack free for one year and one half year respectively, and two were improved.

In addition, Foerster and Penfield (1930) have reported a number of cases operated since them. (The older of these cases may overlap in a few instances the cases above, followed for less than a year.)

In a very carefully and thoroughly studied series of excisions the following results were obtained:

Time post-operatively.	Result.
1) 5 years, 3 months.	Attack free.
2) 5 "	" "
3) 5 "	" "
4) 4 " 6 "	One attack after 4 years, 3 months.
5) 4 " 4 "	Attack free 3 years; isolated absences since.
6) 4 "	Attack free.
7) 3 " 4 "	" "
8) 2 " 7 "	" "
9) 1 " 9 "	" "
10) 1 " 9 "	" "

This group is deserving of mention here, less perhaps because of the statistical results included: three cures of five years duration and three of more than four years: than because of the combination of thorough clinical and histological methods. Its value would be greater if note were made in addition of the cases in which excision therapy failed and the probable reasons for failure.

A modification of the excision method, prompted through fear of severe surgical scarring, is that suggested by the physiologist Trendelenberg. It consists of subcortical section of the fibers running down from the convulsing focus. Fischer (1927) discusses the method. Trendelenberg made deep undercuts half way through the cortex of monkeys and proved a cutting off of the centers. Some months later he

found no scarring, no displacement or macroscopic changes, only a fluid-filled slit. Spielmeyer examined the specimens and found no significant reaction. Fischer does not report a case of traumatic epilepsy treated by this method but does cite six cases of Kirschner's who obtained good results after gunshot wounds, although no note is made of the length of observation.

Mention should be made in passing of Bircher's massage of the epileptic center (Lenormant). Three to five minutes massage of the cortex determines an atrophy of the gray matter which is not followed by the permanent paralyses that are apt to follow excisions done in certain areas. In one epileptic so treated whose brain was studied two months post-operatively the massaged area was found to be 2-3 mms. thick in contrast to the adjacent areas which measured 8-10 mms. Among fourteen cases so treated, six of whom were traumatic in origin, there were two deaths, four failures and eight favorable results - the duration of observation in these last cases was not stated.

The disposal of foreign bodies is a subject upon which there is general agreement. If it be superficial the question may at times be a delicate one, but generally it is better to remove it. A deep lying body is better left alone, unless possibly when it is very large (Lenormant, Buzzard).

Decompression for epilepsy is undoubtedly the oldest of the operative procedures. Reference has already been made to it in the form of trepanation in the historical section. Allen (1906) cites nineteen cases reviewed by Kocher in which pressure upon the dura due to bone, abscess or connective tissue formation was found and removed. 68.3% of cures ~~were~~ was obtained. If the dura was opened in addition the percentage rose to 88.8%. However, Kocher considered only the immediate post-operative results. He credits Bergmann with twenty operations and six cures, or if a three year limit be accepted, with four cures - an operative result of 20%.

Kocher and his pupils Beregowsky and Ito based their operation upon the principle of a safety valve control of hypertension (Lenormant). Cerebro-spinal fluid hypertension is, however, a far from constant finding. Bier bandaged the necks of ten patients, thereby increasing the pressure. There resulted temporary improvement in six; only one suffered aggravation of his attacks. Redlich and Karplus studied a number of war wound epileptics and found either a normal cerebro-spinal fluid pressure or one insignificantly increased. Lenormant concludes, "In practice, the decompressive trepanation of Kocher has given very inconstant results; sometimes negative, sometimes favorable. The indications for the operation are certainly rare in traumatic epilepsy, however they do exist in certain cases of generalized convulsions without localizing symptoms and in which lumbar puncture has shown a hypertension." More recently Leriche and Wertheimer (1925) have shown the pressures in traumatic epileptics to vary either side of the norm, and they have further indicated a less radical means of controlling these changes.

Here it may be mentioned that Schönbauer feels that the best results in desperate cases follow wide decompression made at the time of operation. Foerster removes the bone completely from over the operative site. Penfield, while replacing the flap, always leaves a generous decompression.

Lenormant discusses the question of closure of cranial defects. He advises caution because, although cases have been reported that have become attack free after closure of a defect, on the other hand closure of the skull has sometimes precipitated attacks in cases previously free of seizures. He suggests the following principles: (1) In cases without previous defect it is legitimate to close the skull again after finding and treating the osseous, meningeal or cerebral condition. (2) In cases with loss of bony substance at the time of wounding or of early treatment the indications for closure are fewer. It should not be done for two years, and never if the cerebro-spinal fluid pressure remains high. (3) Decompression he reserves only for those cases with no demonstrable lesion, or with consistently high pressures not relieved by lumbar puncture, or for cases not relieved at previous operations.

Of seventy-four non-epileptics in Steinhal and Nagel's series upon whom decompression operation was performed, fifteen cases later developed epilepsy. In forty-six epileptics drawn from the entire group the operation was successful in twenty-two.

Allen (1906) closed the skull of four patients with seizures by an osteoplastic flap made up of the outer table of an adjacent area. The first case had two seizures in the next year and a half, after having endured more frequent seizures for nine years prior to the operation. A second case, injured seven years before but having attacks only for a week before operation, was attack free for two and a half years, except for a short period immediately post-operative. The third case, kicked on the head by a horse fifteen months prior to operation and having seizures for eleven months before intervention, had but one attack in the year following operative interference. The fourth case, a severe head injury, had had no seizures the first year after operation.

Gamberini (1921) operated upon one hundred and thirty-eight of six hundred and fifty-two war wounds of the skull. Epilepsy later developed in forty-four among those traced to date, in ten not till after an interval of two or three years. He operated anew in thirty-three cases with resultant cure (duration not given), five were materially improved, thirteen were not benefited. He felt that he obtained the best results with an autoplastic flap of bone and periosteum turned down from the adjacent area. The elasticity and yielding nature of the repair gives, he asserted, a safety valve action. In criticism of this last statement may be mentioned Allen's finding that fibrous union in such a flap is firm at five months in experimental animals, and our own finding in the present experimental series (Monkey # 4232) of a very firm union of the bone flap turned down for operative approach four weeks before. There could have been very little, if any, safety valve action in this case.

Operative Mortality.

Figures upon the mortality for all types of operation prior to the World War were gathered by Lenormant. Tilmann in twenty operations of his own lost one case; in his collected statistics including two hundred and sixty operations there were sixteen deaths, a mortality of 6%. In the figures of the Russo-Japanese War reported by Eguchi in 1913 there was one death, two years post-operatively, among eleven operations. Rauch in 1913 reported one death in thirteen operations, four of which were for traumatic cases. Kurt Matthioe in the same year reported three hundred and twenty-six operations with nineteen deaths - 5.7%. Two hundred and sixty-six of these were done for Jacksonian epilepsy, sixteen deaths; sixty for idiopathic cases, three deaths. Lenormant points out that such figures are misleading for they do not take into account the severity of the operation. He quotes from Braun:

73	interventions	(for bone conditions alone)	2 deaths	2.7%
84	"	(meningeal, no brain procedure)	7 "	8.3%
57	"	(cerebral procedure)	8 "	14.0%
32	"	(no appreciable pathology)	2 "	6.2%

Of post-war results he mentions Guelke's series of about fifty cases with no operative mortality.

Among Leriche and Wertheimer's eighteen cases there were two deaths. One, immediately post-operative, was the result of intra-ventricular hemorrhage following opening of the ventricle. The second case developed a cerebral abscess fifteen months later, was relieved by operation, but at the end of the second year died of encephalitis.

Of the eighteen traumatic cases reported by Foerster in 1925 two cases died, one at operation, the second later of abscess, a mortality of 11.1% Among the thirty-five operations reported by Rosanoff the same year there were three deaths, a mortality of 8.6%

Operative Results.

Lenormant considers Matthioe's series of 1913 to be the best studied of the pre-war cases. It was based on three hundred and twenty-six cases.

1. Jacksonian epilepsy.	Favorable results. 81	21 cures, 5 years or over.	
		136 " 1-5 years.	
		19 improvements.	
266 operations.		5 recurrences, after cures or prolonged improvements.	
124 patients followed.			
	Failures. 43	42 stationary.	
		1 aggravation.	
2. Generalized epilepsy.	Favorable results. 15.	3 cures, 5 years or over.	
		4 " 1-5 years.	
		8 improvements.	
60 operations.			
34 patients followed.			
	Failures. 19	17 stationary.	
		2 aggravations.	

The table includes 60% favorable results for the group. In addition to the twenty-four five-year cures cited above there were nine other five-year cures. König claimed two, Bircher one of eleven years duration, Tuffier one of eleven years standing and Auvray reported five.

Steinhal cites Braun's peace time statistics gathered from the results of many surgeons. Among them were one hundred and twenty-eight successful operations and one hundred and eighteen without result, 49% failures. Braun cautions that probably the list of failures is not complete, all the cases not having been reported. It was largely on the basis of such figures that at the German Surgical Congress in 1920 Guelke, Lexer, Küttner and Krause all spoke of the poor operative results achieved, Krause querying that if the peace time results are so poor what will be those of the war wound cases with their worse prognosis.

Among thirty-two cases with brain scarring included in Steinhal's own group there were six cures, and fifteen cases without improvement or with some betterment. Melzner's seventy-six cases, including thirty-seven war wounds, were cited with the observation that Melzner considered the operative results unsatisfactory, although no figures were given.

Schönbauer summarized the forty cases of traumatic epilepsy in his group as follows: eighteen bettered through one or more operations, two died as the result of operation, seven were unharmed, seven died a shorter or longer time after the operation, and seven cases were not benefited. Allowing for the seven cases unharmed or dead, satisfactory results were obtained in 45% of the cases.

Conclusions.

The opinions of Steinhal and Schönbauer represent the most recent thought upon the subject of operative intervention. That of the former is particularly weighty because of his wide experience. Manifestly the results of surgical interference are far from satisfactory. Steinhal is hopeful of the results to be reported from Foerster's clinic. The indications are, however, from the results that Foerster has already reported and from those which Penfield has obtained, that while excision of cortical scars achieves striking results in many cases, perhaps in a higher percentage than has been attained by other procedures, the method is not perfect and leaves much to be desired.

This account leads but further to the view that a satisfactory operative attack upon the problem of traumatic epilepsy must depend upon an understanding of the abnormal physiologic mechanism of the attack. The opinion is hazarded that a vasomotor instability of the cerebral vessels offers the best field for experimental investigation. Whether or not results obtained in such a field of inquiry might be applicable to the problems of idiopathic epilepsy, must remain a matter of conjecture.

Principles of Cerebral Healing.

The principles underlying the healing of brain wounds have been clearly defined since the introduction of the silver staining technique as applied to the study of the interstitial cells of the central nervous system. For a complete presentation of these principles reference should be made to Del Rio-Hortega and Penfield (1927), Penfield (1927), Penfield and Buckley (1928). Only a brief reference to them will be made here.

Following the infliction of a stab wound involving the meninges and brain substance there is called forth a phagocytic reaction of the microglia which persists as long as freshly damaged cerebral tissue is present or as long as progressive deterioration, sometimes extending over many years, goes on (Foerster and Penfield 1930). Soon after the infliction of the wound, - within a few days in animals - the supporting astrocytes hypertrophy and group themselves in a radial fashion about the wound tract. Meantime a connective tissue core grows down into the wound tract. This core is derived chiefly from the mesodermal pia-arachnoid and its different embryologic origin from the ectodermal astrocytes should be borne in mind. If the break in dural continuity has not been repaired following the wounding, the connective tissue scar also has origin in part from the overlying muscle or areolar tissue.

It is by contraction of the connective tissue core of the wound, acting as it does through the vas•astral framework with which it is so intimately connected, that displacement of brain tissue occurs with consequent changes in ventricular topography (Foerster 1925).

On the other hand Penfield and Buckley have demonstated that, in contrast to the histological changes following blunt needle punctures of the brain, an entirely different microscopic picture results if a core of cerebral tissue be removed with a hollow exploratory needle. In such cases there is little or no devitalized tissue to call forth astrocytic response, the hollow space left fills with fluid and there is only the slightest ingrowth of connective tissue elements into the track. There results no cerebral distortion in such cases.

The extension of these principles to neurosurgery is obvious. To quote from Penfield (1927), "It would seem that a contracting scar from brain injury must eventually destroy a larger portion of cerebral tissue than would be destroyed by the initial removal of an equal portion of brain. Also the slow contraction of such a scar, continuing as it does for years, must produce a constant irritation which may well be the starting point for a nervous discharge resulting in Jacksonian epilepsy. Clean excision of such a cicatrix should convert a contracting scar into a fluid-filled space and relieve the remainder of the brain from abnormal contraction." Steinhal (1929), failing to consider the histologic evidence of progressive deterioration in brain wounds, overlooks, it

would seem, the importance of cerebral scarring as an etiologic agent in late epilepsy following trauma.

One of the objectives sought in the present study was confirmation or contradiction of the above conjecture of Penfield concerning the conversion of a cicatrix into an innocuous fluid-filled space. Throughout the literature on the surgical handling of brain wounds there is much difference of opinion upon the end-result of excision of cerebral substance, but little concrete information. The observations of Penfield and Buckley upon healing after puncture with hollow brain needles needed extension to gross removal of cerebral substance. In the present series gross injuries and gross excisions in cats and in monkeys have been studied and contrasted.

In considering the operative treatment of brain scars the reaction of the meninges to operative interference must also be considered. If simple decompression is done and the dura opened without damage to the underlying leptomeninges, little or no adhesion between dura and arachnoid occurs in some cases. In a single decompression done as a control in the present series of monkeys, however, dural thickening and rather dense meningo-cerebral adhesions occurred. Portions of the dura may even be excised and substitution will be made for the defect by a connective tissue layer lined on the under-surface with arachnoid-like cells. In cases of decompression the dural repair is generally of tougher consistency than the original dura, apparently a mechanism to compensate in part for the lack of bony covering. Under a bone flap

dural regeneration is less vigorous. In one case in the present experimental series there was failure of the dura to close a two millimeter gap left at operation because the edges could not be completely approximated.

Frequent attempts, by the introduction of organic and inorganic substances, have been made to prevent the adhesions resulting between the dura and arachnoid (Lenormant 1921). Living grafts of many sorts have been employed, chiefly fascial and fat transplants. If the pia has been unharmed such procedures are unnecessary, for the dura will regenerate spontaneously (Penfield 1927), though possibly not always under a bone flap. If the pia-arachnoid has been injured the transplants only come to be incorporated in the scar tissue and are therefore useless. It would seem that the prevention of meningo-cerebral adhesions can only be hoped for when a technique of handling pia-arachnoid without injury can be developed, a surgical feat which would seem, in the light of present knowledge, to be humanly impossible.

The correction of the dural defect by the incorporation of plates into the cut dural edges has been attempted. The only benefit to be derived from such a procedure is a breaking of the continuity of pull between the scalp and the brain wound - a benefit of hypothetical but entirely unproven value (Sargent 1921). The adhesions between dura and pia are in no way lessened; rather, the transplant becomes firmly enveloped in a connective tissue scar of

great density. More effective than the plate is a closely fitting bone flap which calls forth a less active connective tissue response and which prevents an invasion of the cerebral cicatrix by extra-cranial vessels.

Further reference will be made to these matters in a later chapter when an attempt will be made to outline principles of technical importance.

EXPERIMENTAL METHODS

As outlined in the Introduction the experimental objectives sought were manifold. First it was desired to make a comparative study of the effect upon the post-operative doses of convulsant drugs in animals with brain wounds as one group, and in animals with excisions of corresponding areas in another group. This has been done in cats with camphor and wormwood, in monkeys (Macacus rhesus) with camphor. In addition, excisions of scarred areas have been attempted in monkeys.

Secondly it was expected that the animals under investigation would be sacrificed and the operative sites studied histologically for structural characteristics and for determination, if possible, of the presence or absence of nerve fibers. As the work has gone on, however, the value of keeping some of the animals for a prolonged period of observation has become manifest. Hence not all of the operated specimens are available for study. Furthermore, the determination of the presence or absence of vasomotor nerve fibers awaits further study and will be incorporated in a later report from the Department. The microscopic reports of the structural characteristics of ~~the~~ many scars and excisions are, however, given here.

Thirdly, operative attacks upon the vasomotor supply to the head were planned. This portion of the work cannot be included here and mention is made of it only for the sake of completeness and because of the fact that in the protocols there will be included some animals deprived of their cervical sympathetics upon both sides.

Methods of producing experimental convulsions.

In humans, convulsions follow brain injury in a small proportion of cases. Sauerbruch (1913) found that spontaneous convulsions followed some time post-operatively in a few of his monkeys. Pavlov (1927) reports a number of spontaneous convulsions after cerebral operations performed during the study of conditioned reflexes. On the other hand Muncie and Schneider (1928), Dandy and Elman (1925) and others have not observed spontaneous convulsions in their experiments, though they followed their operated animals for a shorter time post-operatively. Nevertheless, it was felt that an accessory convulsant must be used.

Among the possible means of producing convulsions, other than trauma, are the following:-

1. Anaemia of the brain. Leonard Hill (1896).
2. Asphyxia of the brain due to venous engorgement.
3. Convulsant drugs.
4. Electrical stimulation of the central nervous system.
5. Alkaline diets.
6. Increase of intracranial pressure.
7. Freezing of the cerebral cortex with carbon dioxide. Speransky (1922).
8. Injection of blood into the sub-arachnoid space. Bagley (1928).
9. Alcohol.
10. Fatigue.
11. Decreased oxygen tension. Syz (1926).
12. Oedema of the brain.

Of all this group drugs suggested themselves as being the easiest of control and administration. Many pharmocologic convulsants are available and have been used by different investigators, among them the following:-

1. Camphor.
2. Homocamfin. (Lennox, Nelson and Beetham 1929).
3. Absinthe. (Marce 1864, Horsley 1892, Pike and Elsberg 1925).
4. Thujone. (Cobb 1924, Uyematsu and Cobb 1922). (Florey 1925)
5. Oil of wormwood. (Florey 1925, Dandy and Elman 1925, Muncie and Schneider 1928).
6. Cocaine. (Sauerbruch 1913)
7. Quinine Sulphate.
8. Picrotoxin.
9. Acid Fuchsin (Syz 1927).
10. Amyl Nitrate.
11. Insulin. (Abel 1929).

From this group camphor, $C_{10}H_{16}O$ was chosen as one of the convulsants to be used. Of its action Cushny (1924) says, "The convulsions in mammals are certainly not due to any action on the spinal cord, but to stimulation of the higher areas of the nervous axis. The cerebral cortex is involved in the action for the convulsions are less marked on its removal; but in the lower mammals the chief action seems to be exerted on the nervous centers situated between the cerebral peduncles and the medulla oblongata. It is not improbable that in man the cerebral action may be more marked than on the lower areas, for on descending lower in the scale it is found that cerebral action becomes less evident, thus in birds the removal of the cerebrum seems to have no effect on the convulsions."

(That there is some evidence of a basilar ganglion action in monkeys will be indicated in the protocols.) The drug was used in 20% saline in olive oil. It kept well and there is no reason to feel that its strength varied.

For the purpose of comparison thujon, an isomer of camphor, was used in the form of absinthe and in the form of oil of Wormwood. In the earlier stages of our work it was impossible to obtain absinthe in any form. Finally some essence of absinthe cultivess was obtained from France. This was given intravenously to the monkeys in increasing doses. No convulsions were produced and finally one monkey passed a grossly bloody urine which gave additional evidence microscopically of an acute nephritis. It was assumed that the convulsant was responsible and its use was abandoned. Through the courtesy of Professor Pike of Columbia University we obtained some of the Oil of Absinthe with which he has carried out his many experiments. It was found impossible to give this drug (diluted one to nineteen in 95% alcohol) with any degree of success into the small veins of the monkey and repeated cutting down on the veins over a long period of time presented many difficulties. Therefore as high as ten times the dose was given intramuscularly, but with no effect. Its use was then given up. The oil, as given undiluted by Horsley, we found too difficult to graduate - the reason why Pike diluted it in alcohol.

Oil of Wormwood, used by Dandy and his fellow workers, we were anxious to try for comparison. Because it was available 5% solutions in acacia were used in the earlier experiments, and 10% solutions as used by Dandy were employed later. Two and a half times the convulsant dose for cats, when given to monkeys by stomach tube, led to vomiting but not convulsions. Therefore the drug was used only in the cat experiments. There the convulsant dose for normal animals was found to be satisfactorily constant. The results for the operated animals will be found below.

Originally the camphor was given to the cats intraperitoneally. It was soon found that the cat's peritoneum, ordinarily so hard to infect, was readily susceptible to bacterial invasion in the presence of the ~~intaking~~ irritating camphor. The drug when given intramuscularly thereafter was found to be effective in the same doses, and to be effective in a very similar period of time. Therefore, in most of the experiments, both on cats and on monkeys, camphor was given intramuscularly. Always the buttock was shaved and the skin prepared with iodine and alcohol. In no instance was there an infection. Very occasionally encystment of the camphor was noted in both cats and monkeys, apparently never affecting the results.

The period of observation of the cats after dosing with camphor always lasted eight hours after the last animal was dosed. Many times some of the animals were watched ten, twelve and even fifteen hours after dosing. Only a very occasional convulsion was seen in the later hours, and on some few occasions convulsions

were seen the day after dosing. These convulsions were rare, however, and too infrequent to affect the general results. Occasionally unilateral convulsions were seen twenty-four hours after dosing, or even later.

Wormwood by stomach tube was found to act more readily, and after eight hour periods of observation in the earlier determinations the time was cut to four hours.

For some reason camphor is effective earlier in the monkey than in the cat. Four hours was decided upon as the minimum period for these animals. Rarely a convulsion was seen before the fourth hour, never later, despite frequent opportunity for observation of a late attack.

Operative Procedures:

All the operative work was carried out with the greatest attention possible in animal work being paid to asepsis. The operative technique was exactly that used in the neurosurgical theater with only a few exceptions. Sterlization and preparations of supplies were in the hands of a graduate nurse. The efforts to secure asepsis were well rewarded, for among the sixteen operated cats but one gross infection occurred - directly attributable to faulty draping of the operative field. Two other slight wound infections occurred. Among the many monkeys operated upon one developed an operative infection apparently due to some slip in technique. A second infection occurred late in another animal whose wound opened a week after operation. Infection must, of course, be considered as a complicating factor in cerebral wound healing, as in healing elsewhere in the body.

Cat Operations:

Wounds: A trephine opening in the skull was enlarged to the proper size with rongeurs. The dura was opened and a dural hook, pair of scissors, or some other sharp instrument was inserted into the cerebral substance - the attempt always being made to simulate as closely as possible the destructive effect of a head trauma. In most instances the dura was thereafter carefully sewn together again, at other times it was deliberately left open. The loose areolar tissue was then sewn in a layer and a final closure of the skin made. Collodion dressings almost always remained in place and proved to be very satisfactory.

Excisions: The same type of opening was made as in the case of the wounds. When the area to be extirpated was decided upon it was surrounded by deep sutures on all sides, the sutures were carefully tied so as to cut the cerebral tissue and gather together, but not cut, the blood vessels incorporated in the ligature. The block of tissue was then carefully lifted and dissected out at the bottom with a brain spoon. In some few cases the block was lifted out without the setting of sutures. An attempt was always made carefully to close the dura. In a few instances due to bulging of the brain and the delicacy of cat dura, the closure was impossible. Such instances are noted in the protocols. In a few cases fascial transplants were incorporated in the dural closure.

Monkey Operations:

Wounds: The procedure followed was exactly that in the case of wounds in cats except in one instance (#4215) when a bone flap was fashioned. In monkeys the dura is much heavier and easier to handle than in cats, so that a good closure was invariably obtained when desired. In two or three instances the dura was intentionally left open in the hope of promoting adhesions.

Excisions: In this group bone flaps were turned down, a small Gigli saw being used in the fashioning of the flap. In all the cases in this series the dura was carefully closed. The bone flaps were secured by the use of heavy silk ties in place of silver wire. One of these cases developed a wound infection, presumably due to a slip in technique rather than to contamination by the monkey itself. In a second case trephine buttons included in the closure were not vascularized and acted as foreign bodies, causing the wound to break down. In two instances old wounds produced in the manner described above were excised - in these cases there was no bone flap available to cover the excised area and no attempt was made to perform an osteoplastic operation in either instance.

Anaesthesia:

A few of the earlier operations upon cats were performed under ether anaesthesia. The later ones were all done under amytal anaesthesia - .6 to .7 cc. of the 10% solution per kilo was the usual dose. All of the operations upon monkeys were carried out under amytal and the drug proved to be a most satisfactory one for

them. In doses of .6 cc. per kilo, occasionally supplemented by a little more amytal or by ether, a very satisfactory anaesthesia permitting of faradic stimulation of the brain was obtained. In no case were untoward effects observed and in no instance did the intraperitoneal injection of the drug cause trouble. (The abdomen was always shaved, then prepared with 7% iodine followed by alcohol. The injections were made into the lower abdomen, the needle never was pointed upward.)

Care of the animals:

The cats were kept in large, divided cages permitting of exercise. They were amply fed upon milk and a good grade of raw beef. With the exception of a few months during the winter when, dring the readjustment following a fire, they were in a room with only one window, they had abundant fresh air. The monkeys did not live under ideal conditions during the winter and spring, having both insufficient air and sunlight. With the coming of the summer months, however, they were gotten out into the open air in a cage atop their house. Tuberculosis was rampant among them, as is so frequently the case with captive monkeys. In contrast to the cats who gained weight, the monkeys maintained, in most instances, lost in some few instances, their weight upon acquisition. In neither the cats nor the monkeys did slight variations in quality and quantity of food affect the minimum convulsant dose.

The cats had very frequent and sometimes severe colds during the winter months following the fire. Despite this fact, and the acidosis presumably accompanying, the convulsant dose seemed to vary little. In one cat with a chronic ear infection the convulsant threshold was somewhat low (#4226). Three cats passed through pregnancy and lactation without definite effect on their minimum convulsant threshold. Another cat, acquired and dosed a few days after delivery, had a high threshold (#4204), but as it persisted after involution and cessation of lactation, other causes of the increased tolerance must have existed.

Establishment of the Minimum Pre-operative Convulsant Dose in Cats.

In the earlier work, carried on in the fall of 1929, two groups of cats were dosed with camphor. Group 1. below is the first of these and is made up of a series of thirty cats. It had a mortality of 100%, the deaths being due to intercurrent infections, to ether anaesthesia, or occasionally amytal, and to fire. Group 2. is made up of nine cats which came to operation, all of which were wiped out by a laboratory fire. A third group of animals ~~were~~ was started as controls early in 1930, their records are to be found under Group 3. In this group camphor, wormwood and absinthe were used interchangeably.

Wormwood Oil, 5% suspension in gum acacia, given by stomach tube, was used originally. Later 10% solution was used, as done by Dandy. Since the dose of the 5% solution was established as twice that of the 10%, within the limits of experimental error, all the results are expressed in terms of the 10% solution for purposes of comparison with Dandy's results. As noted above the monkeys were unable to retain by stomach a sufficient amount of the 5% solution to produce convulsions, they being more resistant to the convulsant than cats. Therefore the results with wormwood apply only to the cats. The control cats dosed with wormwood all belong to Group 3, - many of them were dosed with wormwood, absinthe and camphor interchangeably. The detailed figures of the doses for these animals are to be found in the protocols.

Summary of Group 1. (complete summary protocols are omitted)

Total number of cats - 30.
Dose definitely established in 16 at:

1.5 cc in two cats, one of which was dosed by peritoneum.
1.6 cc " two " two " " were " " "
1.7 cc " six " four " " " " " "
1.8 cc " five " three" " " " " "
1.9 cc " one cat...

Two cats showed a reversal of their doses, thus

4133:	Date:	Weight:	Dose:	Total:	Result:	Convulsant:	Days:	Remarks:
	11/2	2.0	x 1.7	3.4 cc	(0)			
	11/5	1.7	x 1.8	3.0 cc	Status and death.			
4155:	12/17	3.5	x 1.7	6.0 cc	(2)(2)			
	12/20	3.6	x 1.8	6.5 cc	(2)			

Twelve cats died for one of a number of reasons before their doses could be established. It is important to note that of these two had had their doses raised to high levels: one to 2.4 cc/Kg, the second to 2.1 cc/Kg, without ensuing convulsions.

Conclusions to be drawn from Results of Group 1.

1. The average minimum convulsant dose of sixteen normal cats was 1.70 cc/Kg.
2. In a series of thirty cats the doses of sixteen were established at this level. In two the minimum convulsant dose was something greater than 2.4 and 2.1 cc/Kg. In two others there was an insignificant reversal of the doses.
3. The intra-peritoneal and intra-muscular doses are identical.

Group 2. (Made up of cats whose doses were established, who were operated upon, but who were killed by fire before the post-operative doses could be established).

No:	Date:	Weight:	Dose:	Total:	Result:	Convulsant:	Days:	Remarks:
4094:	9/29	3.55	x 1.7:	6.0	(1)	C.		
	12/12	Death - 71 days post-operatively.						
4099:	10/16	2.5	x 1.7:	4.2	(0)	C.		
	10/17	2.5	x 1.8:	4.5	(0)			
	10/23	2.5	x 1.9:	4.7	(0)			
	10/25	2.7	x 1.8:	5.2	(2)			
	12/12	Death - 44 days post-operatively. (Minimum convulsant dose 1.8 cc)						
4101:	10/23	2.9	x 1.7:	5cc(?)	(0)	C.		4.5 cc given intra-per.
	10/25	3.1	x 1.7:	5.2	(0)			
	10/31	3.1	x 1.8:	5.5	(2)			
	12/12	Death - 42 days post-operatively. (Minimum convulsant dose 1.8 cc)						
4104:	10/25	4.1	x 1.7:	6.9	(0)	C.		
	10/31	4.2	x 1.8:	7.5	(3)			
	11/12	3.8	x 1.7:	6.5	(0)i.p.			
	12/12	Death						
4108:	11/8	2.9	x 1.7:	4.9	(2)i.p.	C.		Seizure next a.m. (2)
	11/15	2.9	x 1.6:	4.6	(1)i.p.			
	11/19	3.1	x 1.6:	5.0	(2)i.p.			
	12/12	Death - 21 days post-operatively. (Minimum convulsant dose 1.6 cc)						
4109:	11/8	2.1	x 1.7:	3.5	(0)i.p.	C.		
	11/15	2.5	x 1.8:	4.5	(0)i.p.			
	11/19	2.2	x 1.9:	4.2	(0)i.p.			
	11/22	2.2	x 2.0:	4.4	(2)i.p.			
	12/12	Death - 9 days post-operatively. (Minimum convulsant dose 2.0 cc)						
4111:	11/2	3.5	x 1.7:	5.9	(1)i.p.	C.		
	11/5	3.4	x 1.6:	5.5	(1)(2)i.p.			
	12/12	Death - 36 days post-operatively. (Minimum convulsant dose 1.6 cc)						
4117:	11/15	2.8	x 1.7:	4.8	(2)i.p.	C.		
	12/12	Death - 24 days post-operatively. (Minimum convulsant dose 1.7 cc)						
4120:	11/21	1.7	x 1.7:	2.9	(2)i.p.	C.		
	12/12	Death - 20 days post-operatively. (Minimum convulsant dose 1.7 cc)						
4126:	11/26	2.2	x 1.7:	3.8	(2)i.p.	C.		
	12/12	Death - 13 days post-operatively. (minimum convulsant dose 1.7)						

Summary of Group 2.

Total number of Cats - 9.
Dose definitely established in 9 at:

1.6 in two cats.
1.7 " three "
1.8 " " "
2.0 " one cat

Among this group two cats showed a slight but insignificant reversal of dose similar to that noted in Group 1. above.

Conclusions to be drawn from the results of Group 2.

1. The average dose of nine normal cats prior to operation was 1.74 cc/Kg.

Perusal of the above tables suggests two considerations. The first concerns itself with the occasional variation from the general average minimum convulsant doses. The second is suggested by the relatively small number of doses given over a short period of time. To secure further data upon the behaviour of camphor frequently repeated, and to provide an adequate control between normal and operated animals through all seasons of the year, Group 3. of the control cats was established. Opportunity was provided in this group, furthermore, of studying the effect of one convulsant upon the animal's susceptibility to another; an important control inasmuch as the operated cats were shifted from camphor to wormwood and back again

Group 3.

No:	Date:	Weight:		Dose:	Total:	Result:	Convulsant:		Days:	Remarks:
4162:	1/13	3.1	x	1.7:	5.4	(0)		C.		
	1/15	2.9	x	1.8:	5.3	(0)			2 days.	
	1/21	2.6	x	1.9:	4.9	(0)			8 "	
	1/24	2.6	x	2.0:	5.2	(0)			11 "	
	2/7	2.9	x	2.1:	6.1	(0)			25 "	
	2/11	3.1	x	2.2:	6.8	(0)			29 "	
	2/21	3.6	x	2.3:	8.3	(0)			39 "	
	3/6	3.7	x	2.5:	9.2	(0)			52 "	
	3/11	3.7	x	2.6:	9.6	(2)			57 "	
	3/20	3.8	x	2.6:	9.9	(0)			66 "	
	3/27	3.6	x	2.7:	9.8	(0)			73 "	
	4/3	3.7	x	2.9:	10.9	(0)			80 "	
	4/18	3.5	x	2.0:	7.0	(0)		W.	95 "	
	4/21	3.6	x	2.5:	9.0	(0)			98 "	
	4/24	3.5	x	3.1:	11.0	(3)		C.	101 "	
	5/29	2.7	x	2.6:	1.0	(0)			146 "	
	6/5	3.0	x	3.1:	9.3	(2)			153 "	
	6/10	2.9	x	2.1:	6.1	(0)	plus.	W.	158 "	
	6/19	3.2	x	2.2:	7.2	(0)			167 "	
	7/7	3.2	x	2.5:	8.0	(2)	plus-plus		185 "	
	7/22	Total dose not given.								
	7/25	3.9	x	2.3:	9.0	(3)		W.	188 "	
	8/4	3.8	x	2.2:	8.4	(3)			198 "	
	8/8	3.4	x	1.9:	6.5	(0)			202 "	

Summary:

Camphor - minimum convulsant dose - about 3.1 cc/Kg.
(high and unreliable)

Wormwood - 2.2 cc/Kg.

No:	Date:	Weight:	Dose:	Total:	Result:	Convulsant:	Days:	Remarks:
4189:	2/7	4.1 x	1.7:	7.0	(0)	C.		
	2/11	4.3 x	1.8:	7.7	(0)		4 days.	
	2/21	4.0 x	1.9:	7.6	(3)		14 "	
	3/15	4.3 x	1.8:	7.7	(0)		36 "	
	3/20	4.7 x	1.9:	8.9	(2)		41 "	
	4/3	5.0 x	1.9:	9.6	(3)		55""	
	4/18	5.0 x	1.0:	5.0	(0)	W.	70 "	
	4/21	5.0 x	1.3:	6.7	(0) plus		73 "	
	4/24	4.9 x	1.5:	7.3	(0)		76 "	
	5/1	4.6 x	2.0:	9.3	(3)		83 "	
	5/5	4.4 x	2.0:	8.9	(2)(0plus)		87 "	
	5/14	4.5 x	1.7:	7.8	(0)		96 "	vomited.
	5/17	4.3 x	1.7:	7.6	(0)		99 "	vomited.
	5/29	4.0 x	1.9:	7.6	(2)		111 "	
	6/5	4.3 x	1.9:	8.2	(2)	C.	118 "	
	6/10	4.6 x	1.8:	8.3	(2)		123 "	
	6/19	4.6 x	1.9:	8.7	(0) plus	W.	132 "	
	7/7	4.3 x	1.9:	8.2	(0)		150 "	
	7/22	Not dosed.						
	7/25	4.8 x	2.1:	10.1	(0)		153 "	
	8/4	4.4 x	2.1:	9.2	(3) plus-plus		163 "	
		Note: 5 days prior to this dosing this cat was under full amytal anaesthesia and a temporal fascia transplant was taken. Possibly this accounts for the change in reaction?						
	8/8	4.5 x	1.9:	8.5	(0)	W.	167 "	

Summary:

Camphor - minimum convulsant dose 1.8 cc/Kg.
Wormwood - " " " 2.0 cc/Kg.

No:	Date:	Weight:		Dose:	Total:	Result:	Convulsant:	Days:	Remarks:
4190:	2/7	3.1	x	1.7:	5.3	(1) plus	C.		
	2/11	3.1	x	1.8:	5.6	(0)		4 days.	
	2/21	3.2	x	1.9:	6.1	(0)		14 "	
	3/11	3.4	x	2.0:	6.9	(0)		32 "	
	3/15	3.3	x	2.2:	7.4	(2)		36 "	
	3/20	3.3	x	2.2:	7.3	(0)		41 "	
	3/27	3.4	x	2.3:	7.8	(0)		48 "	
	4/3	3.4	x	2.4:	8.2	(0)		55 "	
	4/18	3.3	x	1.0:	3.3	(0)	W.	70 "	
	4/21	3.3	x	1.5:	4.9	(3)		73 "	
	4/24	3.2	x	2.5:	8.1	(0)	C.	76 "	
	5/29	3.2	x	1.7:	5.4	(0)		111 "	
	6/5	3.3	x	2.6:	8.6	(0)		118 "	
	6/10	3.2	x	1.5:	4.8	(0)	W.	123 "	
	6/19	3.5	x	1.9:	6.6	(0)		132 "	
	7/7	3.4	x	2.0:	6.8	(2) plus-plus-plus		150 "	
	7/22	3.3	x	1.8:	5.9	(2)		165 "	
	7/25	3.5	x	2.6:	9.1	(2) plus-plus	C.	168 "	
	8/4	3.3	x	2.3:	7.6	(2)		178 "	
	8/8	3.4	x	1.6:	5.4	(0)	W.	182 "	

Summary:

Camphor - minimum convulsant dose - unreliable, varying between 1.7 and 2.6 cc/Kg.
Wormwood - minimum convulsant dose 1.8 cc/Kg.

No:	Date:	Weight:	Dose:	Total:	Result:	Convulsant:	Days:	Remarks.
4196:	2/21	4.0 x	1.7:	6.8	(0)	C.		
	3/15	4.3 x	1.8:	7.9	(0)		22 days	
	3/20	4.3 x	1.9:	8.3	(2)		27 "	
	3/27	4.1 x	1.8:	7.4	(0)		34 "	
	4/3	4.5 x	1.9:	8.5	(0)		41 "	
	4/18	4.7 x	1.1:	5.1	(0)	W.	56 "	
	4/21	4.9 x	1.5:	7.3	(0)		59 "	
	4/24	4.8 x	2.0:	9.6	(0)	C.	62 "	
	5/1	4.6 x	1.6:	7.4	(0)	W.	69 "	
	5/29	4.0 x	1.9:	7.6	(0)	C.	97 "	
	6/5	4.4 x	2.2:	9.7	(0)	C.	104 "	
	6/10	4.5 x	2.4:	10.8	(3)		109 "	
	6/19	4.7 x	2.0:	9.4	(2)plus	W.	118 "	
	7/7	4.4 x	1.9:	8.3	(0)		136 "	
	7/22	4.5 x	2.0:	9.0	(0)		151 "	vomited.
	7/25	4.6 x	2.0:	9.2	(0)		154 "	
	8/4	4.5 x	2.2:	9.9	(2)		164 "	
	8/8	4.2 x	2.0:	8.4	(0)		168 "	

Summary:

Camphor - variable - minimum convulsant dose 1.9 to 2.4 cc/Kg.
Wormwood - 2.2 cc/Kg.

No:	Date:	Weight:	Dose:	Total:	Result:	Convulsant:	Days:	Remarks:
4197:	3/11	4.3 x	1.7:	7.4	(2)plus	C.		
	3/15	4.4 x	1.6:	7.0	(2)		4 days.	
	3/20	4.3 x	1.6:	6.9	(2)		9 "	
	3/27	4.3 x	1.5:	6.5	(0)		16 "	
	4/3	4.4 x	1.6:	7.0	(0)plus		23 "	
	4/18	4.4 x	1.2:	5.5	(0)plus	W.	48 "	
	4/24	4.3 x	1.5:	6.5	(0)		54 "	
	5/1	4.3 x	1.7:	7.4	(0)		61 "	not dosed.
	5/5	4.2 x	2.0:	8.4	(0)plus		65 "	
	5/14	4.0 x	2.2:	7.8	(0)		74 "	vomited.
	5/17	4.0 x	2.1:	8.4	(0)		77 "	vomited.
	5/29	4.0 x	2.0:	8.0	(2)		89 "	vomited.
	6/5	3.5 x	2.0:	7.1	(2)		96 "	
	6/10	4.0 x	2.0:	8.0	(2)		101 "	
	6/19	4.4 x	1.9:	8.4	(2)		110 "	
	7/7	4.3 x	1.9:	8.2	(2)		128 "	
	7/22	4.3 x	1.8:	7.9	(2)plus		143 "	
	7/25	4.6 x	1.6:	7.4	(2)	C.	146 "	
	8/4	4.4 x	1.7:	7.5	(2)	W.	156 "	
	8/8	4.5 x	1.5:	6.8	(2)		160 "	

Summary:

Camphor - minimum convulsant dose - 1.6 cc/Kg. reliable.
Wormwood - " " " 1.7 cc/Kg.

No:	Date:	Weight:		Dose:	Total:	Result:	Convulsant:	Days:	Remarks:
4204:	4/18	4.0	x	.16:	.64	(0)	A.		
	4/24	3.9	x	1.7:	6.7	(0)	C.	6 days.	
	5/1	3.9	x	1.8:	7.0	(0)		13 "	
	5/5	3.7	x	2.0:	7.4	(0)		17 "	
	5/14	3.6	x	2.4:	8.6	(2)plus		26 "	
	5/17	3.4	x	2.2:	7.5	(0)		29 "	
	5/29	3.2	x	1.9:	6.0	(0)plus		41 "	
	6/5	3.1	x	2.3:	7.1	(0)		48 "	
	6/10	3.2	x	2.0:	6.4	(0)	W.	53 "	
	6/19	3.6	x	2.1:	7.5	(0)		62 "	vomited.
	7/7	4.0	x	2.2:	8.8	(0)		80 "	vomited.
	7/22	3.9	x	2.4:	9.4	(2)		95 "	
	7/25	3.8	x	2.4:	9.1	(2)plus-~~plus~~	C.	98 "	
	8/4	3.5	x	2.2:	7.7	(2)		108 "	
	8/8	4.0	x	2.2:	8.8	(0)	W.	112 "	

Summary:

Camphor - minimum convulsant dose - 2.2 cc/Kg.
Wormwood - " " " 2.3 cc/Kg.

No:	Date:	Weight:		Dose:	Total:	Result:	Convulsant:	Days:	Remarks:
4206:									
	4/18	1.9	x	.06:	.12	(0)	A.	8 days.	i.v.
	4/21	1.9	x	.07:	.14	(0)		11 "	i.v.
	5/1	1.9	x	.99:	1.9	(0)		19 "	i.m.
	5/5	2.1	x	2.9:	6.2	(0)		23 "	i.m.
	5/14	2.3	x	.09:	.20	(0)		32 "	i.v.
	5/17	2.0	x	1.2:	.24	(2)plus-plus-plus		35 "	undiluted.
	6/5	2.0	x	2.0:	4.0	(2)plus	W.	54 "	
	6/10	2.1	x	1.9:	4.0	(0)		59 "	
	6/19	1.9	x	1.8:	3.5	(2)		68 "	
	7/7	2.2	x	1.8:	3.9	(0)		86 "	
	7/22	2.4	x	2.0:	4.8	(2)plus-plus		101 "	
	7/25	2.5	x	1.7:	4.2	(0)	C.	104 "	
	8/4	2.6	x	1.9:	4.9	(0)plus		114 "	
	8/8	2.6	x	1.8:	4.7	(0)	W.	118 "	

Summary:

Camphor - minimum convulsant dose - somewhat greater than 1.9cc/Kg
Wormwood - " " " 1.9 cc/Kg.

No:	Date:	Weight:		Dose:	Total:	Result:	Convulsant:	Days:	Remarks:
4207:	4/18	3.6	x	.06:	.24	(2)	A.		i.v.
	4/21	3.8	x	.06:	.23	(0)		3 days.	i.v.
	5/1	3.8	x	.99:	3.8	(0)		11 "	i.m.
	5/14	3.8	x	.07:	.26	(0)		24 "	i.v.
	5/17	3.6	x	.07:	.27	(1)		27 "	i.v.
	5/29	3.3	x	.07:	.25	(2)		39 "	i.v.
	6/5	3.3	x	.07:	.23	(0)		46 "	i.v.
	6/5	3.3	x	2.0:	6.6	(3)	plus-plus W.		
	6/10	3.4	x	1.8:	6.3	(2)		51 "	
	6/19	4.0	x	1.8:	7.2	(2)		60 "	
	7/7	4.5	x	1.8:	8.1	(3)	plus-plus-plus	78 "	
	7/22	4.3	x	1.7:	7.3	(0)	plus	93 "	
	7/22	4.5	x	1.6:	7.2	(2)	plus C.	96 "	
	8/4	4.5	x	1.4:	6.4	(3)		106 "	
	8/8	4.5	x	1.6:	7.2	(2)	plus-plus-plus W.	110 "	

Summary:

Absinthe - minimum convulsant dose - .066 of 1 part of Oil of Absinthe in 19 of 95% alcohol intravenously.
Camphor - minimum convulsant dose - less than 1.4 cc/Kg.
Wormwood - " " " " " 1.7 cc/Kg.

No:	Date:	Weight:		Dose:	Total:	Result:	Convulsant:	Days:	Remarks:
4208:	4/18	2.8	x	.06:	.19	(3)	A.		i.v.
	4/21	2.9	x	.06:	.17	(0)		3 days	i.v.
	5/1	2.8	x	1.9:	5.6	(0)		11 "	i.m.
	5/14	2.9	x	.06:	.17	(0)		24 "	i.v.
	5/17	2.8	x	.06:	.18	(0)		27 "	i.v.
	5/29	2.7	x	.07:	.18	(0)		39 "	i.v.
	6/5	2.7	x	.07:	.20	(0)		46 "	
	6/10	2.8	x	.20:	?	(0)		51 "	
	6/19	3.0	x	2.0:	6.0	(2)	W.	60 "	
	7/7	3.0	x	2.0:	6.0	(2)		78 "	
	7/22	3.1	x	2.0:	6.2	(0)		93 "	vomited.
	7/25	3.8	x	1.8:	7.6	(2)	C.	96 "	
	8/4	3.2	x	1.6:	5.1	(0)		106 "	
	8/8	3.4	x	1.8:	6.1	(0)	W.	110	

Summary:

Camphor - minimum convulsant dose - 1.8 cc/Kg.
Wormwood - " " " 2.0 cc/Kg.

No:	Date:	Weight:	Dose:	Total:	Result:	Convulsant:	Days:	Remarks:
4224:	5/1	2.5 x	1.8:	4.6	(0)	W.		
	5/5	2.4 x	2.1:	5.0	(0)		4 days.	
	5/14	2.7 x	2.3:	6.3	(2)plus		13 "	
	5/17	2.6 x	2.2:	5.8	(2)		16 "	
	5/29	2.6 x	2.1:	5.5	(0)		28 "	
	6/5	2.6 x	2.1:	5.6	(2)		35 "	
	6/10	2.9 x	2.4:	7.0	(2)	C.	40 "	
	6/19	2.9 x	2.1:	6.1	(0)	W.	49 "	
	7/7	2.8 x	2.1:	5.9	(3)		67 "	
	7/22	2.9 x	2.0:	5.8	(0)		82 "	
	7/25	3.0 x	1.9:	5.7	(2)	C.	85 "	
	8/4	3.9 x.	1.7:	6.6			95 "	complete dose not given.
	8/8	3.0 x	2.0:	6.0	(0)	W.	99 "	

Summary:

Camphor - minimum convulsant dose - 1.9 cc/Kg.
Wormwood - " " " 2.1 cc/Kg.

No:	Date:	Weight:	Dose:	Total:	Result:	Convulsant:	Days:	Remarks:
4225:	5/1	2.9 x	2.0:	5.9	(0)	W.		vomited.
	5/5	2.8 x	2.2:	6.3	(2)(Gplus)		4 days.	
	5/14	2.9 x	2.1:	6.1	(2)		13 "	
	5/17	2.8 x	2.0:	5.6	(0)		16 "	
	5/29	2.8 x	2.1:	5.9	(2)plus-plus.		28 "	
	6/5	2.8 x	2.0:	5.9	(2)plus-plus-plus.		35 "	
	6/10	2.8 x	2.0:	5.6	(2)		40 "	
	6/19	3.1 x	1.9:	6.0	(2)		49 "	
	7/7	3.0 x	1.9:	5.9	(0)		67 "	
	7/22	3.2 x	2.0:	6.4	(2)plus-plus-plus		82 "	
	7/25	3.4 x	1.6:	5.4	(2)	C.	85 "	
	8/4	3.7 x	1.4:	5.2	(0)plus		95 "	
	8/8	3.4 x	1.8:	6.1	(2)	W.	99 "	

Summary:

Camphor - minimum convulsant dose - 1.5 cc/Kg.
Wormwood - " " " 1.9 cc/Kg.

No:	Date:	Weight:		Dose:	Total:	Result:	Convulsant:	Days:	Remarks:
4226:	5/1	2.8	x	2.0:	5.6	(0)	W.		
	5/5	2.7	x	2.2:	6.2	(2)plus		4 days.	
	5/14	2.9	x	2.1:	6.1	(2)plus		13 "	
	5/17	2.8	x	2.0:	5.6	(2)		16 "	
	5/29	2.7	x	2.0:	5.4	(2)		28 "	
	6/5	2.7	x	1.9:	5.1	(2)		35 "	
	6/10	2.9	x	1.8:	5.1	(2)		40 "	
	6/19	3.0	x	1.7:	5.1	(2)plus-plus		49 "	
	7/7	3.0	x	1.6:	4.8	(2)		67 "	
	7/22	3.0	x	1.5:	4.5	(0)		82 "	vomited.
	7/25	3.2	x	1.6:	5.1	(2)	C.	85 "	
	8/4	3.3	x	1.4:	4.6	(2) plus		95 "	
	8/8	3.6	x	1.4:	5.0	(2)	W.	99 "	

Summary:

Camphor - minimum convulsant dose - less than 1.4 cc/Kg.
Wormwood - " " " " " 1.4 cc/Kg.

Conclusions to be drawn from the results of Group 3.

1. In those cases where the camphor dose was around the average which had been obtained in the first and second groups above, it tended to remain at that level for a few repetitions of the dose, and thereafter might or might not remain constant.
2. In some cats whose resistance to camphor was high, convulsions were not obtained till after several doses of camphor had been given. Therefore it is likely that the minimum convulsant dose established in these animals is unreliable.
3. Except in those instances in which the cat reacted by convulsive seizures early in the series of dosings and was thereby grouped roughly at its proper convulsant level, the results with camphor as a convulsant have been totally unreliable. This observation will be confirmed in the protocols of the operated cats to be given below.
4. Camphor (10% solution in olive oil) is not a convulsant drug which can be used over a period of time, to follow variations in the convulsant threshold. Its employment for this purpose should be abandoned.
5. Oil of Wormwood in 10% solution in gum acacia, given by stomach tube, can be used to follow variations in convulsant threshold. In control animals the threshold remains practically unchanged when repeated over long periods.

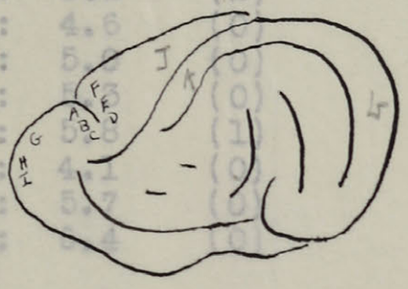
6. In general, a cat which reacts reliably on a relatively low camphor dose reacts on a low wormwood dose, and vice versa. This observation is made use of in discussing the protocols of the operated cats, for in them only camphor was used as a pre-operative convulsant. Yet it is felt that as they all reacted at about the average convulsant threshold for camphor on the first or second dosing, their wormwood convulsant threshold can also be considered to be the average for wormwood - despite the fact that this was not actually proven pre-operatively.

Establishment of Post-operative Doses in Cats.

For clarity of exposition the establishment of the pre-operative doses of camphor for these animals has been witheld and complete protocols will be given for each of the animals immediately below.

The operations performed fall into two classes - wounds and excisions. The wounds were performed in such a fashion as to simulate severe head injuries. The excisions were in each instance an attempt to remove cerebral tissue with as little damage to tissue as possible. In performing these operations the principles detailed in the section on wound histology were constantly borne in mind; the dura was carefully folded back, the block excision was done as cleanly as possible and the dural repair made with all care. In some instances a satisfactory dural closure was not made - such cases are always noted.

The Cat's Brain



modified from
Muncie and Schneider

A,B,C and D,E,F lie on either side of the cruciate sulcus and mark the location of the motor zone.

G,H,I designate the frontal pole which is in reality of smaller proportions than drawn.

J and K mark the area in the parietal region in which wounds and excisions of designation were made, with the exception of #4103 in which case the excision was made further back, over the parietal eminence.

L represents the site of occipital wounds, amputations included the entire pole.

Note: In the protocols the following abbreviations are used:

Ess. of A. --- Essence of Abinthe Cultive
A. --- Oil of Absinthe (Pike), 1 part in 19 parts of 95% alcohol
C. --- 20% Camphor in olive oil
W. --- Oil of Wormwood, 10%, in gum accacia.

Adult female.

4134: Motor cortex injury: (J.P.E) Dural hook inserted in the region of the cruciate sulcus and moved about. Pia-arachnoid scarified. Circular area of dura removed from over wound.

Date:	Weight:	Dose:	Total:	Result:	Convulsant:	Days:	Remarks:
12/5	2.2 x	1.7:	3.7	(2)plus-plus	C.		i.p.
12/10	2.1 x	1.5:	3.2	(2)			i.p.
2/3	3.1 x	1.5:	4.6	(0)		51	
2/18	3.1 x	1.6:	5.0	(0)		66	
2/21	3.1 x	1.7:	5.3	(0)		69	
3/6	3.2 x	1.8:	5.8	(1)		82	generalized.
3/11	3.2 x	1.3:	4.1	(0)		87	
3/15	3.2 x	1.8:	5.7	(0)		91	
3/20	3.2 x	2.0:	6.4	(0)		96	3/22 Jacksonian attack; rt.eyelid.
3/27	3.1 x	2.2:	6.9	(0)		103	
4/3	3.2 x	2.5:	8.0	(2)		110	generalized.
4/15	3.2 x	2.5:	8.0	(0)		122	
4/24	3.1 x	2.6:	8.1	(3)		131	generalized.
6/3	3.6 x	2.6:	9.5	(2)plus-plus-plus		171	Not lateralized
6/4				(2)		172	Not lateralized but followed by twitching of rt. eyelid.
6/12	3.6 x	2.0:	7.2	(2)		180	Not lateralized
6/21	3.7 x	1.5:	5.6	(0)		189	
6/24	3.5 x	1.0:	3.5	(2)	W.	192	Rt.sided body turning, tho bilateral.
6/28	3.8 x	.7:	2.6	(2)plus		196	Not lateralized
7/18	3.6 x	.4:	1.5	(0)		216	
7/23	3.7 x	.5:	1.8	(2)plus		221	Bilateral.
7/28	3.6 x	.3:	2.2	(0)		226	
8/1	3.6 x	.4:	1.4	(2)		230	Bilateral onset
8/6	3.5 x	.2:	.7	(0)		235	

Summary of Dosing: Pre-operative camphor dose established at 1.5 cc/Kg. The post-operative camphor dose was found to be 2.0, of wormwood .4 That is, the camphor dose was raised .5, the wormwood dose lowered 1.6

Histology: Muscle firmly adherent to the underlying arachnoid. There is an extensive connective tissue ingrowth into the wound track with a freer invasion of capillaries from the scar into the surrounding cerebral tissues than is usually seen in the case of a sulcus.

The picture is that of a typical brain wound resulting from inclusion of devitalized brain tissue. (Photograph)

4136: Large female.
Motor cortex injury: (J.P.E). Dura over cruciate sulcus removed Dural hook inserted into the motor area and moved about freely. Pia-arachnoid scarified in same area.

Date:	Weight:	Dose:	Total:	Result:	Convulsant:	Days:	Remarks:
12/10	3.4 x	1.7:	5.8	(2)	C.		i.p.
2/3	3.6 x	1.7:	6.1	(0)	C.	52	Unilateral convulsions on 2/6
2/18	3.4 x	1.5:	5.1	(0)		67	
2/21	3.4 x	1.6:	5.5	(0)		70	
3/6	3.6 x	1.7:	6.1	(0)		83	
3/11	3.1 x	1.8:	6.5	(0)		88	
3/15	3.6 x	2.0:	7.2	(0)		92	
3/20	3.5 x	2.2:	7.7	(0)		97	
3/27	3.6 x	2.2:	7.9	(0)		104	
4/3	3.5 x	2.5:	8.9	(0)		111	
4/15	3.6 x	2.8:	9.2	(3)		123	Rt. sided onset.
4/24	3.6 x	2.7:	9.8	(0)		132	Paretic rt rear
6/3	3.8 x	2.8:	10.6	(2)plus		172	Head & body to right.
6/12	3.9 x	2.5:	9.7	(2)		181	Jacksonian attack, rt. sided then generalized
6/21	3.9 x	2.0:	7.8	(0)		190	
6/24	3.8 x	1.0:	3.8	(0)	W.	193	
6/28	3.8 x	1.5:	5.8	(2)plus		197	Not lateralized
7/18	3.8 x	1.2:	4.6	(2)		217	Not lateralized
7/23	3.8 x	1.0:	3.8	(1)		222	Not lateralized
7/28	3.9 x	1.8:	6.2	(2)		227	Jacksonian at onset; poor control of rt. foreleg rt rear after attack
8/1	4.0 x	.6:	2.4	(2)		231	Head to rt. at onset.
8/6	4.1 x	.4:	1.6	(0)		236	

Summary of Dosing: Pre-operative camphor dose established at 1.7 cc/Kg. The post-operative camphor dose was found to be 2.5, of wormwood .9 That is, the camphor dose was raised .8, the wormwood dose was lowered 1.1

Histology: The picture is that of a typical wound reaction with a heavy connective tissue core penetrating down to the white matter.

4150: Young female.
Parietal wound: (J.P.E) Dura over parietal eminence incised, dural hook inserted a distance of a few mms. and moved about freely. Exposed brain scarified. Dura not closed.

Date:	Weight:	Dose:	Total:	Result:	Convulsant:	Days:	Remarks:
12/14	2.2 x	1.7:	3.7	(3)plus	C.		i.p.
12/17	2.0 x	1.6:	3.2	(2)			i.p.
2/17	3.0 x	1.7:	5.1	(0)		61	
3/6	3.3 x	1.8:	6.2	(0)		78	
3/11	3.4 x	2.0:	6.8	(2)		83	generalized
3/15	3.4 x	1.9:	6.5	(0)		87	
3/20	3.2 x	2.1:	6.7	(0)		92	
3/27	3.2 x	2.2:	7.1	(0)		99	
4/3	3.3 x	2.5:	8.2	(0)plus		106	
4/15	3.4 x	2.7:	9.2	(2)plus		118	Not lateralized
4/24	3.3 x	2.7:	8.9	(3)		127	
6/3	3.7 x	2.7:	10.1	(2)plus		167	Not lateralized
6/12	4.0 x	2.4:	9.6	(0)		176	
6/21	3.9 x	1.0:	3.9	(0)	W.	185	
6/24	3.8 x	1.5:	5.7	(3)		188	Bilateral.
6/28	3.9 x	1.2:	4.7	(2)		192	Bilateral.
7/18	4.0 x	1.0:	4.0	(0)		212	
7/23	3.9 x	2.0:	7.9	(0)	C.	217	
7/26	Sacrificed.						

Summary of Dosing: Pre-operative camphor dose established at 1.6 cc/Kg The post-operative camphor dose was found to be 2.7 of wormwood 1.2 That is, the camphor dose was raised 1.1, the wormwood dose lowered .8

Histology: The dura is absent from the section. The picture is one of atypical wound reaction with heavy penetration of connective tissue fibers and capillaries well into the white matter. At the brain surface there is the usual arachnoid proliferation and the inclusion of large numbers of phagocytic cells.

4160: Adult female.
Frontal pole wound: (J.P.E) Dural hook inserted just behind cruciate sulcus and projected forward. Pole macerated. Dura in region of cruciate sulcus left opened and turned back.

Date:	Weight:	Dose:	Total:	Result:	Convulsant:	Days:	Remarks:
1/9	3.2 x	1.7:	5.4	(1)	C		
2/21	3.4 x	1.7:	5.8	(0)		38	
3/6	3.4 x	1.9:	6.5	(0)		51	
3/11	3.5 x	2.1:	7.3	(0)		56	
3/15	3.4 x	2.3:	7.9	(0)		60	
3/20	3.3 x	2.5:	8.2	(0)		65	
3/27	3.4 x	2.7:	9.1	(0)		72	
4/3	3.3 x	2.9:	9.6	(0)		79	
4/15	3.2 x	3.1:	9.9	(0)		91	
4/24	3.1 x	3.3:	10.2	(0)		100	
6/3	3.6 x	3.5:	12.6	(0)		140	Pregnant.
6/12	3.8 x	3.7:	14.1	(0)		149	
6/24	3.7 x	1.5:	5.6	(2)	W.	161	Bilateral.
6/28	4.0? x	1.0:?	4.0	(2)		165	Bilateral, vomited.
7/18	3.2 x	.7:	2.2	(0)		185	Nursing.
7/23	Not dosed - nursing.						
7/28	3.5 x	1.8:	5.6	(2)		195	Bilateral.
8/1	3.5 x	.7:	2.4	(0)plus		199	

Summary of Dosing: Pre-operative camphor dose established at 1.7 cc/Kg The post-operative camphor dose was found to be something over 3.7, of wormwood .8 That is, the camphor dose was raised over 2.0 cc, the wormwood dose was lowered 1.2

Histology: Dura adherent, cystic arachnitis, typical wound reaction extending down from a fluid-filled space opening at the brain surface. There is extension of the connective tissue into the white matter.

4167: Adult female.
Frontal lobe wound: Dura opened at cruciate sulcus. Dural hook inserted, pushed forward, and the frontal pole extensively macerated. Dura left open.

Date:	Weight:	Dose:	Total:	Result:	Convulsant:	Days:	Remarks:
1/4	3.1 x	1.7:	5.3	(0)	20% camphor in neat's foot oil		i.p.
1/9	3.2 x	1.9:	6.0	(2)			
2/21	3.6 x	1.9:	6.8	(0)		41	
3/6	4.1 x	1.9:	8.0	(0)		54	
3/11	3.8 x	2.1:	8.0	(0)		59	
3/15	3.8 x	2.3:	8.8	(0)		63	
3/20	3.9 x	2.5:	9.7	(0)		68	
3/27	3.8 x	2.7:	10.2	(0)		75	
4/3	3.9 x	2.9:	11.3	(0)		82	
4/15	3.8 x	3.1:	11.7	(0)		94	
4/24	3.7 x	3.3:	12.2	(0)		103	
4/25				(S)		104	Jacksonian rt. face.
6/3	3.5 x	3.3:	11.5			144	Status - Jacksonian attacks beginning rt. eyelid or rt. ear - then generalized.
6/12	3.4 x	2.7:	9.3	(0)		153	
6/24	3.3 x	1.5:	5.0	(3)plus	W.	165	Not lateralized
6/28	3.5 x	1.0:	3.5	(2)plus-plus-plus		169	Head to rt. at onset in most attacks.
7/18							
7/23	3.3 x	.5:	1.7	(0)		194	
7/28	3.4 x	1.7:	4.8	(3)		199	Not lateralized
8/1	3.4 x	.5:	1.7	(0)		203	

Summary of Dosing: Pre-operative camphor dose established at 1.9 cc/Kg The post-operative camphor dose was found to be 3.3, of wormwood .6 That is, the camphor dose was raised 1.4, the wormwood dose lowered 1.4

Histology: There is a deep and extensive wound, the contents of which have in large part been lost. There are still present, however, the borders of the wound which are extensively fibrosed. The brain tissue about is degenerated and there is a good deal of phagocytosis still going on.

The picture is one of the usual type in brain wounds.

Note: The upper ventricular system was found to be symmetrically dilated in this animal, apparently a block at the aqueduct of Sylvius being due to an inflammatory reaction possibly caused by intra-ventricular hemorrhage. The dilatation made possible a striking comparison between the two lateral ventricles and demonstrated with great clearness a pulling up of the right ventricle toward the wound. There seems to have been communication between the wound track and the ventricle.

4179: Small adult female.
Occipital pole wound: (J.P.E) Dura opened over tip of occipital pole. Dural hook and scissors inserted deeply. A small piece of muscle forced into the wound. Dura left unclosed.

Date:	Weight:	Dose:	Total:	Result:	Convulsant:	Days:	Remarks:
1/24	2.4 x	1.7:	4.1	(2)	C.		
3/6	2.9 x	1.7:	5.0	(0)		28	
3/11	3.0 x	1.9:	5.7	(0)		33	
3/15	2.9 x	2.1:	6.1	(3)		37	Bilateral
3/20	2.9 x	2.0:	5.8	(0)		42	
3/27	3.0 x	2.1:	6.3	(0)		49	
4/3	3.0 x	2.3:	7.0	(3)		56	Bilateral
4/15	3.2 x	2.2:	7.1	(0)plus		68	
4/24	3.4 x	2.2:	7.5	(0)plus		77	
6/3	3.2 x	2.3:	7.4	(0)		117	Lactating.
6/12	3.4 x	2.4:	8.1	(0)		126	
6/24	3.3 x	1.5:	4.9	(3)	W.	138	Not lateralized
6/28	3.3 x	1.0:	3.3	(0)		142	
7/18	3.2 x	1.2:	3.9	(0)plus		162	
7/23	3.2 x	2.5:	7.0	(0)plus	C.	167	
7/28	Sacrificed.						

Summary of Dosing: Pre-operative dose of camphor established at 1.7 cc/Kg. The post-operative camphor dose was found to be 2.6, of wormwood 1.3 That is the camphor dose was raised 1.9, the wormwood dose lowered .7

Histology: Normal muscular, meningeal and cerebral relationships are preserved till the wound site is reached. At this point there is an indentation of the cerebral tissue in which lies what is presumably the muscle inserted at operation. There is a great deal of connective tissue reaction about it and there is a pronounced musculo-meningeal, cerebral adhesion. From this point downward there is dense connective tissue ingrowth which thins and fans out at the sides. The core itself extends deeply into the cerebrum and just before the level of the white matter is reached there opens out a large cyst lined with a reacting connective tissue and partially filled with debris made up in part of many small capillaries. From the cyst there extends down more deeply into the white matter occasional capillaries and connective tissue strands.

The picture is one of very severe wound reaction. The cellular reaction is quite minimal compared to other wounds in the series of a similar age. Apparently then, the degenerative process has ceased and the scarring is at its height.

4180: Large Tom.
Occipital pole wound: (J.P.E) Scissors and dural hook inserted into tip of occipital pole - macerated. Dura not closed.

Date:	Weight:	Dose:	Total:	Result:	Convulsant:	Days:	Remarks:
1/21	3.7	x 1.7:	6.3	(3)plus.	C.		
1/24	3.7	x 1.6:	5.9	(0)			
3/6	4.8	x 1.7:	8.2	(0)		35	
3/11	4.4	x 1.9:	8.4	(0)		40	
3/15	4.4	x 2.1:	9.3	(0)		44	
3/20	4.4	x 2.3:	10 .2	(0)		49	
3/27	4.6	x 2.5:	11.5	(3)plus.		56	Generalized.
4/3	4.7	x 2.4:	11.4	(0)		63	
4/15	4.7	x 2.6:	11.9	(0)		75	
4/24	4.5	x 2.7:	12.1			84	Occasional jerking rt.face, & rt. leg.
5/1						91	Focal attack with narrowed palpebral fissure. Pupils equal.
6/3	4.8	x 2.7:	13.0			131	Status with Jacksonian pattern. Eyes & head to rt. Rt. foreleg & rt. hind-leg to lt. side.
6/4						132	Jacksonian right eyelid.
6/12	4.7	x 2.0:	9.0	(3)+++		140	Jacksonian onset generally rt.sided - in one instance was lt.sided (exhaustion). In some instances Not lateralized.
6/21	4.3	x 1.4:	6.0	(0)		149	
6/24	4.4	x 1.5:	6.6	(3)plus	W.	152	Jacksonian rt. sided.
6/28	4.6	x .8:	3.7	(0)		156	
7/18	4.1	x 1.1:	4.5	(0)		176	
7/23	4.5	x 1.3:	5.9	(3)+++		181	Jacksonian and non-Jacksonian,
7/28	4.6	x 1.1:	10.1	(0)		186	

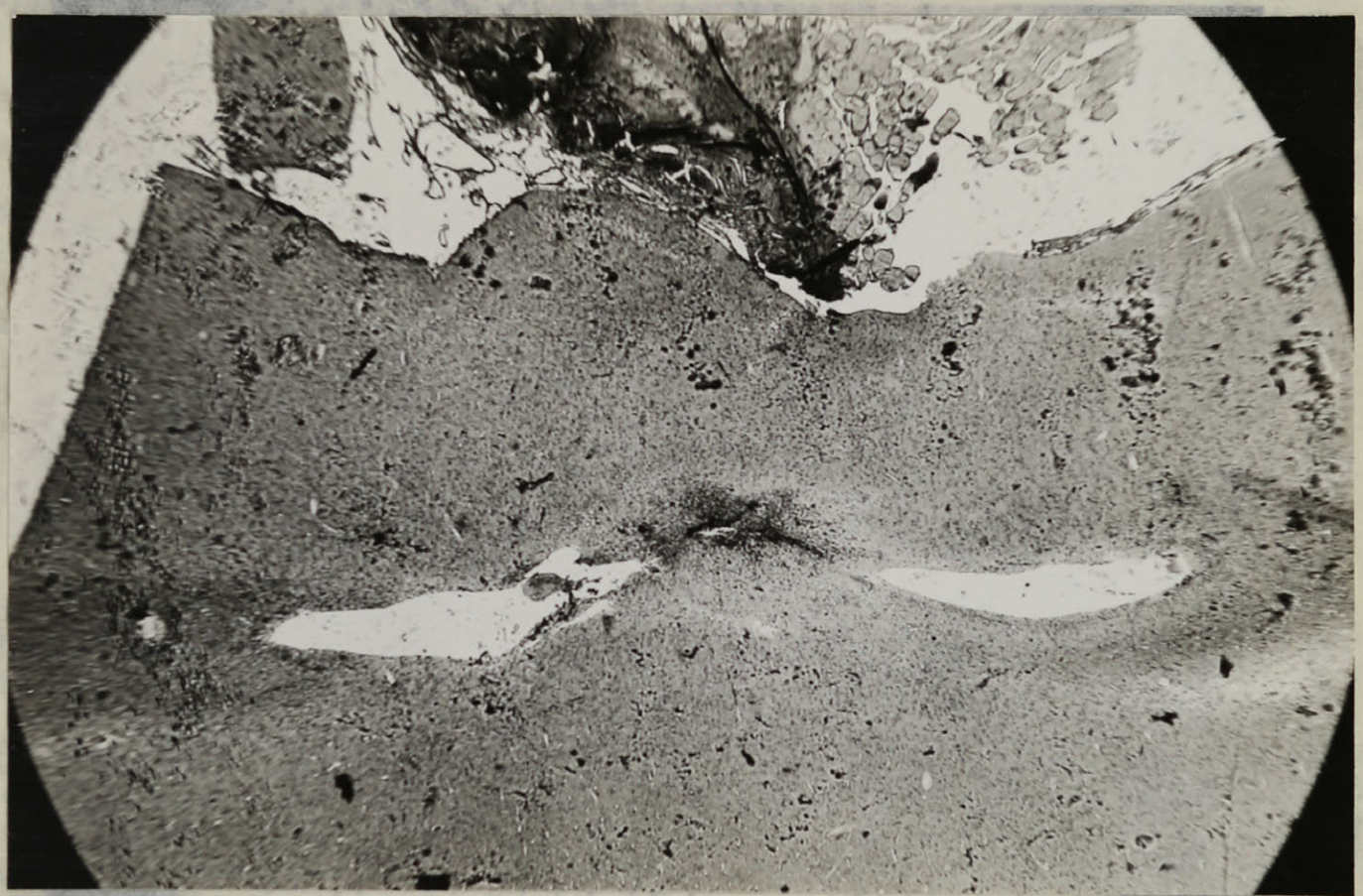
4180: Continued.

Summary of Dosing: Pre-operative camphor dose established at 1.7 cc/Kg. The post-operative camphor dose was found to be irregular, something under 2.0, of wormwood 1.2 That is, the camphor dose was raised about .3, the wormwood dose lowered .8

Histology: Muscle adherent to the meninges which in turn are securely attached to the brain by minute connective tissue projections infiltrating through the sub-pial layer of astrocytes. In the sections studied there was no direct continuity between the surface and cystic area resulting from the wound. This area is made up of two relatively large cysts separated by a reacting zone of very active connective tissue. It may be that this zone bears continuity with the surface, but it is not evident in the sections. There is active phagocytosis going on.

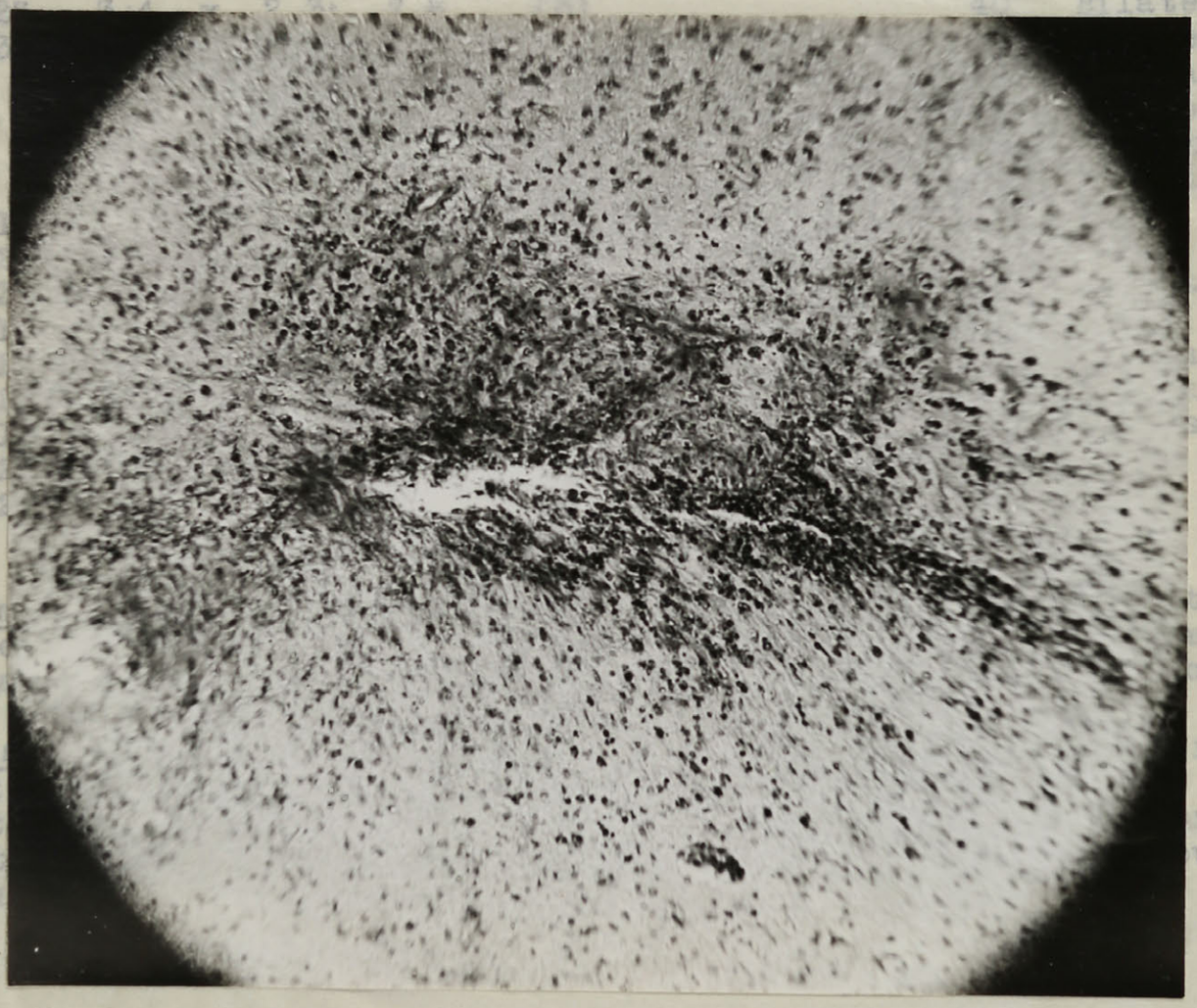
The histologic picture is, then, one of absorption of old damaged cerebral tissue with cyst formation and with a connective tissue and glial reaction of moderate but definite degree. (Photograph).

4180, Cat, Wound



Low power view of an active scarring process accompanied by cyst formation. The connection of the tract with the surface is not shown.

4180, Cat, Wound



A higher magnification of the active scarring shown in the preceding plate. Note the connective tissue proliferation and the presence of phagocytes.

4191: Adult female.
Motor cortex wound: (J.P.E). Dura opened over cruciate sulcus. Scissors and dural hook inserted into post-cruciate sulcus ~~and~~ and destruction proceded with anteriorly.

Date:	Weight:	Dose:	Total:	Result:	Convulsant:	Days:	Remarks:
2/11	3.2 x	1.7:	5.4	(2)			
3/11	3.1 x	1.7:	5.3	(2)	C.	24	Bilateral.
3/15	3.2 x	1.7:	5.4	(0)		28	
3/20	3.1 x	1.8:	5.7	(0)		33	
3/27	3.4 x	2.3:	7.8	(3)		40	Bilateral.
4/3	3.5 x	2.2:	7.7	(2)		47	Bilateral, but with a right rear intermittent tonic extension preceding.
4/15	3.6 x	2.1:	7.6	(0)plus		59	
4/24	3.3 x	2.2:	7.4	(0)		68	
6/3	3.3 x	2.2:	7.3	(2)plus		108	Head to right?
6/12	3.3 x	1.8:	5.8	(0)		117	
6/24	3.1 x	1.5:	4.7	(2)plus	W.	129	Not lateralized.
6/28	3.3 x	1.0:	3.3	(2)		133	Not lateralized.
7/18	3.2 x	.7:	2.2	(2)(0-plus)		153	Not lateralized.
7/23	3.2 x	.4:	1.3	(0)		158	
7/28	3.3 x	.5:	3.3	(0)		163	
	Sacrificed.						

Summary of Dosing: Pre-operative camphor dose established at 1.7 cc/Kg. The post-operative camphor dose was found to be 2.2, of wormwood .6 That is, the camphor dose was raised .5, the wormwood dose lowered 1.4

Histology: A wound track is filled with connective tissue strands but not the usual heavy fibrous core. The process is, however, still very active as indicated by the marked parenchymal degeneration and phagocytosis. There is a good deal of cystic formation throughout the degenerated area.

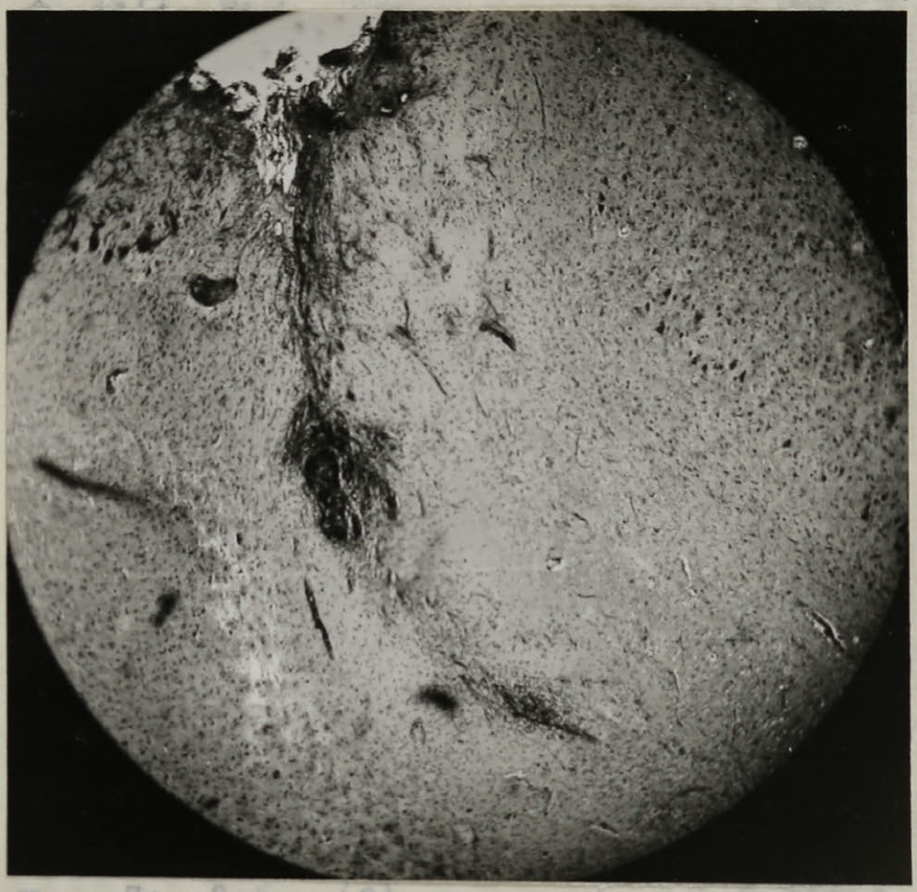
4192: Adult female.
Motor cortex wound: (J.P.E) Exposure over motor area and frontal pole, all of which tissue was macerated. Dura left open.

Date:	Weight:	Dose:	Total:	Result:	Convulsant:	Days:	Remarks:
2/11	2.7 x	1.7:	4.6	(3)	C		
3/11	3.1 x	1.7:	5.3	(0)		22	
3/15	3.1 x	1.8:	5.6	(0)		26	
3/20	3.2 x	1.9:	6.1	(0)		31	
3/27	3.2 x	2.1:	6.7	(1)		38	Late.
4/3	3.2 x	2.2:	7.0	(0)		45	
4/15	3.2 x	2.4:	7.7	(0)		57	
4/24	3.2 x	2.5:	8.0	(0)		66	
6/3	3.2 x	2.5:	8.1			106	Status - Jacksonian in type Rt. eyelid or rt. fore-leg, then spread.
6/4						107	Post-epileptic state.
6/12	3.2 x	1.8:	5.8	(2)plus		115	Not lateralized
6/21	3.3 x	.9:	3.0	(0)		124	
6/24	3.3 x	1.0:	3.3		W	127	Status. Jacksonian in type Discharges fired from both rt. & lt. cortices.
6/28	3.3 x	.5:	1.6	(0)		131	
7/18	3.3 x	.7:	2.3	(0)plus		151	
7/23	3.4 x	1.8:	6.2	(1)plus	C	156	Not lateralized
7/28	Sacrificed.						

Summary of Dosing: Pre-operative camphor dose established at 1.7 cc/Kg The post-operative camphor dose was found to be something under 1.8, of wormwood .9 That is, the camphor dose had remained unchanged, the wormwood dose was lowered 1.1

Histology: Study shows a typical wound track whose base is adherent to the overlying muscle and whose tip extends deeply into the brain, reaching well into the white matter. Scattered here and there through the track are collections of round cells, evidently phagocytes, although relatively few of them are loaded with debris. At the base of the track there are many compound granular corpuscles scattered through the meninges. There is connective tissue penetration for a depth of two to three millimetres over a large portion of the brain surface on either side of the track.

4192, Cat, Wound



A typical scar reaction with inclusion of a heavy connective tissue core. An area of active phagocytosis indicates that the process is still progressive. The meningeal reaction is not shown.

4103 - Adult female.
Left parietal excision: (J.P.E). A block of tissue about 1 x 1 x 1 cms. was removed from near the parietal eminence by use of sutures. Dura closed over excision. (Torn at bottom margin but covered excised area).

Date:	Weight:	Dose:	Total:	Result:	Convulsant:	Days:	Remarks:
10/25	3.8 x	1.7:	6.4	(0)	C.		
10/31	3.7 x	1.8:	6.7	(2)		6 days.	
1/13	3.7 x	1.8:	6.7	(3)plus		72 "	generalized.
2/3	3.8 x	1.7:	6.5	(0)		93 "	
2/18	3.8 x	1.3:	5.0	(2)		108 "	generalized.
2/21	3.7 x	1.3:	4.8	(0)		111 "	
3/6	4.0 x	1.7:	6.9	(0)		124 "	
3/11	3.8 x	1.4:	5.2	(0)		129 "	
3/15	3.7 x	1.9:	7.1	(0)		133 "	
3/20	3.6 x	2.1:	7.6	(0)		138 "	
3/27	3.7 x	2.3:	8.5	(0)		145 "	generalized.
4/3	3.8 x	2.2:	8.4	(0)		152 "	
4/15	3.6 x	2.4:	8.8	(0)		164 "	
				(S) seizure			late.
4/24	3.5 x	2.4:	8.5	(0)		173 "	
6/3	4.1 x	2.5:	10.4	(0)		213 "	
6/4				(R)		214 "	Head to right at onset.
6/12	4.1 x	2.1:	8.7	(1)		222 "	Jacksonian; head & eyes to right rt. fore-leg; then generalized
6/21	4.3 x	1.8:	7.7	(0)		231 "	
6/24	4.1 x	1.5:	6.1	(2)	W.	234 "	Head & eyes rt. side at onset.
6/28	4.3 x	1.0:	4.3	(0)		238 "	
7/23	3.7 x	1.2:	4.4	(2)plus		263 "	Not lateralized
8/1	3.7 x	.9:	3.3	(2)		267 "	Not lateralized
8/6	3.5 x	.7:	2.5	(0)		272 "	

Summary of Dosing: Pre-operative camphor dose established at 1.8 cc/Kg. The post-operative camphor dose was found to be 2.1, the post-operative wormwood dose .9. That is the camphor dose was raised .3, the wormwood dose lowered 1.1

Histology: Not sacrificed -

4105 - Adult Male.
Left Motor Cortex Excision:(J.P.E). Motor cortex excised in a block, by suture method. A small amount of traumatized tissue could not be cleanly removed and was left behind. Dura sewn closely.

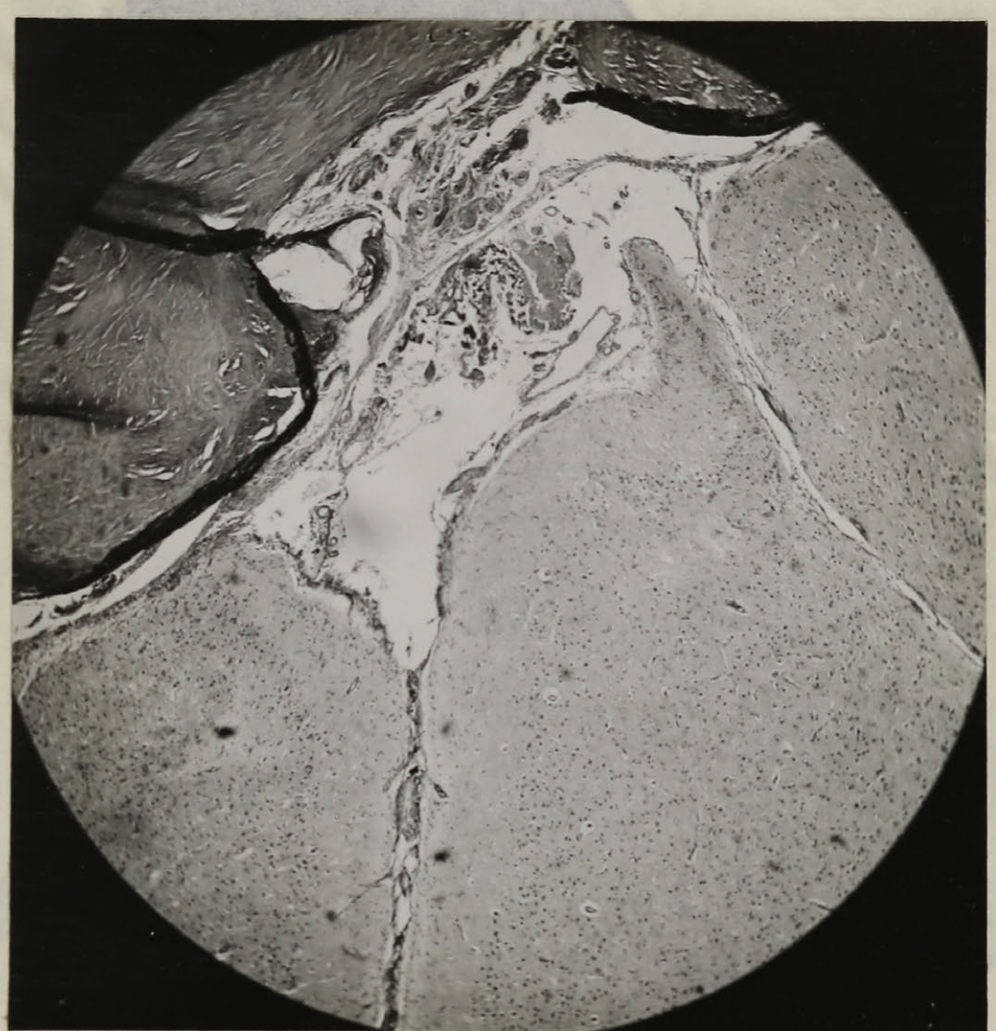
Date:	Weight:	Dose:	Total:	Result:	Convulsant:	Days:	Remarks:
10/25	5.0 x	1.7:	8.5	(2)			
11/12	4.9 x	1.7:	8.4	(3)plus	C.	18 days.	i.p.
2/3	5.2 x	1.7:	8.8	(0)		69 "	
2/18	5.1 x	1.8:	9.2	(0)		84 "	
2/21	4.9 x	2.0:	9.8	(0)		87 "	
3/6	5.2 x	2.2:	11.4	(0)		100 "	
3/11	5.0 x	2.4:	12.0	(0)		105 "	
3/15	4.9 x	2.6:	12.7	(0)		109 "	
3/20	4.7 x	2.8:	13.2	(0)		114 "	
3/27	4.7 x	3.0:	14.1	(0)		121 "	
4/3	4.6 x	3.2:	14.7	(0)		128 "	
4/15	4.7 x	3.3:	15.6	(S)		140 "	
4/24	4.5 x	3.3:	15.0	(S)		149 "	
4/25				(S)		150 "	
4/26						151 "	Paresis at prelg
6/3	4.9 x	3.3:	16.2	(2)		189 "	Head & body to right.
6/4				(2)		190 "	" "
6/12	4.9 x	3.0:	14.7	(2)plus		198 "	" "
6/21	4.7 x	2.4:	11.3	(3)		207 "	
6/24	4.5 x	1.5:	6.7	(0)	W.	210 "	
6/28	4.6 x	1.8:	8.4	(0)		214 "	
7/18	4.8 x	2.1:	10.2	(0)		234 "	vomited.
7/23	4.8 x	2.3:	11.0	Death. S Right sided focal onset.		239 "	

Summary of Dosing: Pre-operative camphor dose established at 1.7 cc/Kg. The post-operative camphor dose was found to be 2.4, of wormwood 2.3 (with resultant death in a convulsion). That is, the camphor dose was raised .7 the wormwood dose raised .3

Histology: Musculo-meningeal - dural adhesion. The excision site is not deep. It is filled in part with a loosely meshed net-work of connective tissue fibers. From it extends down to the grey matter a narrow arm which terminates as a loosely, mildly proliferating connective tissue projection. On the other side of a small adjacent area of degenerative brain tissue is another similar arm with connective tissue projection.

The process is nearly at a standstill judging from the lack of cellular reaction. The picture is that of a very slight reaction to excision (Photograph).

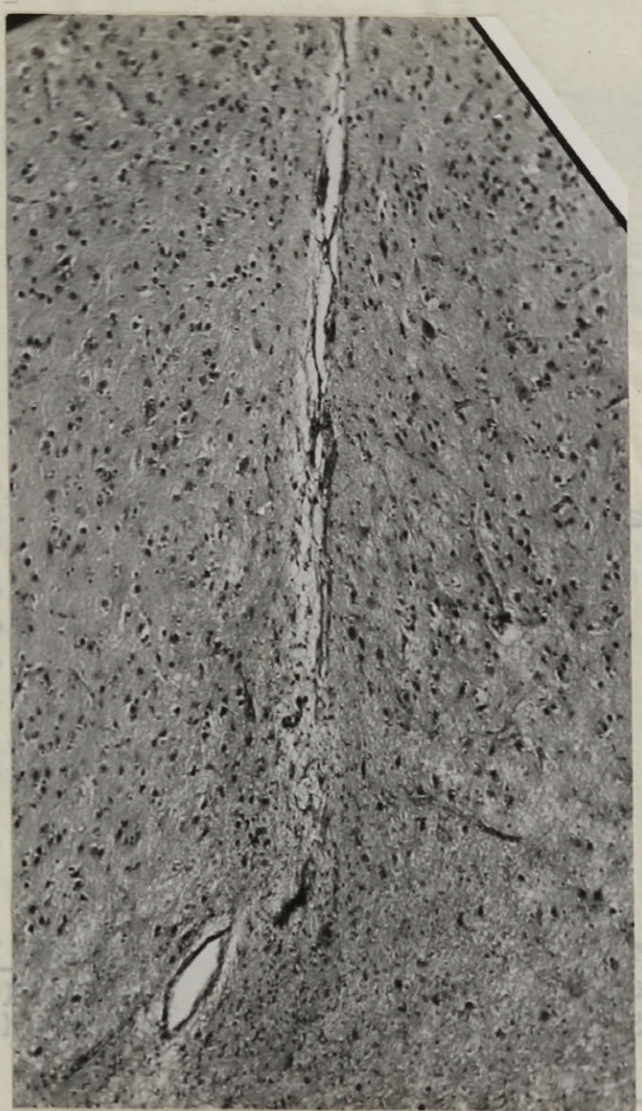
4105, Cat, Excision



Low Power View of the Excision Site

The site is filled with fluid and scattered debris. The musculo-meningeal-cerebral adhesion, a typical finding in both wounds and excisions, is well shown. A comparison of the sulcus on the left with the track on the right which forms a part of the excision reaction indicates the benignness of the process.

4105, Cat, Excision



A higher magnification of the end of the track shown on the right in the preceding picture. Note that it reaches to the white matter.

4135: Adult female.

Left motor cortex excision: (J.P.E). The motor area lying behind the cruciate sulcus with some of the area immediately posterior was cleanly removed en bloc by the suture method. Dura satisfactorily closed.

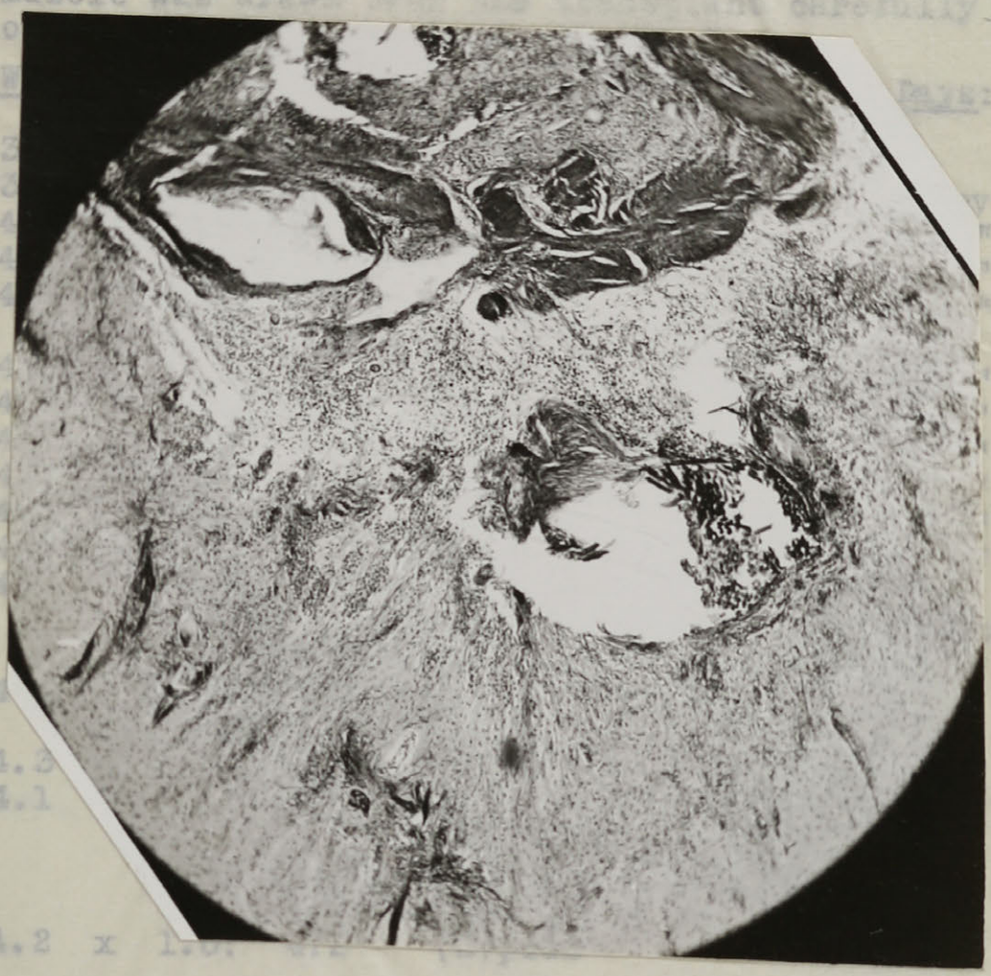
Date:	Weight:	Dose:	Total:	Result:	Convulsant:	Days:	Remarks:
12/5	2.7 x	1.7:	4.6	(2)(1)	C.		i.p.
2/3	3.7 x	1.7:	6.2	(0)		58	
2/18	3.7 x	1.8:	6.7	(0)		73	
2/21	3.6 x	1.9:	6.9	(0)		76	
3/6	4.0 x	2.1:	8.5	(0)		89	
3/11	3.8 x	2.3:	8.8	(0)		94	
3/15	3.7 x	2.5:	9.3	(0)		98	
3/20	3.7 x	2.7:	10.0	(0)		103	
3/27	3.9 x	2.9:	11.3	(3)plus.		110	Not lateralized.
4/3	3.8 x	2.8:	10.8	(0)		117	
4/15	3.8 x	2.9:	11.0	(3)		129	Rt. sided onset-rt. fore-leg.
4/24	3.6 x	2.7:	10.4	(0plus)		138	
6/3	3.6 x	2.9:	10.4	(2)plus-plus		178	Not lateralized.
6/12	3.7 x	2.6:	9.6	(0)		187	
6/21	3.5 x	1.6:	5.8	(2)	W.	196	Bilateral.
6/24	3.5 x	1.3:	4.6	(0)		199	
6/28	3.5 x	1.5:	5.2	(2)		203	Not lateralized.
7/18	3.4 x	1.2:	4.0	(2)		223	Tonic convulsion not lateralized.
7/23	3.3 x	.9:	3.0	(2)		228	Not lateralized.
7/28	3.4 x	.7:	2.4				
8/1	3.3 x	.8:	2.7	(0-plus)		237	Isolated jerks of rt. foreleg.

Summary of Dosing: Pre-operative camphor dose established at 1.7 cc/Kg The post-operative camphor dose was found to be 2.9, of wormwood .8 That is, the camphor dose was raised 1.2, the wormwood dose lowered 1.2

Histology: The muscle over-lying the excision site is densely infiltrated with scavenger cells, presumably called forth by the presence of a bit of the silk suture left at operation. The dura appears to be continuous over the excision site which is filled with a marked connective tissue proliferation. Throughout there are scattered great numbers of scavenger cells. The connective tissue fibers penetrate into the brain substance in great profusion, and interlace freely with glial fibers. The fibrosis and gliosis extend into the white matter. There is no reason to suspect post-operative infection.

In this instance the operative objective was not obtained. The shallow excision area filled with arachnoidal granulation tissue and presumably because of the presence of a foreign body there was an extensive cellular reaction. The net result has been great fibrosis and gliosis (Photograph).

4135, Cat, Excision Failure



Low Power View of the Excision Site

This animal's convulsant threshold was lowered, rather than remaining unchanged or being slightly increased. There is extensive growth of connective tissue into the cerebral substance. Note that the excision was shallow and did not remove grey matter down to the fiber tracts.

4156 - Adult male.
Frontal pole excision: (J.P.E). The entire pole lying anterior to the cruciate sulcus was lopped out without sutures. Bleeding controlled with hot saline. Because of herniation the dura could not be closed. "An unsuccessful attempt was made to insert a satisfactory temporal fascia graft. It could only be attached to the dura at the lateral and mesial borders and it was tucked in over the cut brain surface, between it and the back wall of the frontal sinus. Posteriorly it was left free. The temporal muscle was drawn over the transplant carefully so as not to overly directly the brain tissue."

Date:	Weight:	Dose:	Total:	Result:	Convulsant:	Days:	Remarks:
12/17	3.8 x	1.7:	6.5	(2)plus			i.p.
12/20	3.8 x	1.6:	6.0	(2)plus-plus-plus.	C.	3 days.	i.p.
1/4	4.1 x	1.5:	6.1	(2)		18 "	i.p.
2/21	4.2 x	1.7:	7.1	(3)plus		41 "	
3/6	4.4 x	1.5:	6.6	(0)		54 "	unilateral convulsion 3/7
3/11	4.3 x	1.5:?	6.5?	(0)		59 "	
3/15	4.4 x	~~1.0:~~?	~~7.1~~?	(0)		63 "	
3/20	4.3 x	1.7:	7.4	(0)		68 "	
3/27	4.3 x	1.9:	8.1	(3)		75 "	generalized.
4/3	4.3 x	1.8:	7.7	(2) ~~plus (2)~~		82 "	1st generalized; 2nd onset rt. arm leg then generalized
4/15	4.4 x	1.7:	7.6	(0)		94 "	
4/24	4.2 x	1.8:	7.6	(3)		103 "	
5/1				Questionable Jacksonian attack. Rt. eyelid; Ptosis rt. eyelid.		110 "	
6/3	4.3 x	1.8:	7.7	(2)plus		143 "	Jacksonian onset.
6/12	4.3 x	1.5:	6.5	(0)		152 "	
6/24	4.1 x	1.5:	6.2	(3)	W.	164 "	Began with movements of rt front rt arm. Body turned lt.
6/28	4.2 x	1.0:	4.2	(2)plus		168 "	Rt.sided onset Later tonic turning of head to rt.
7/18	4.0 x	.7:	2.8	(2)		188 "	Not lateralized
7/23	4.0 x	.~~4~~:	1.6	(0)		193 "	
7/26	Sacrificed.						

Summary of Dosing: Pre-operative camphor dose established at 1.5 cc/Kg. The post-operative camphor dose was found to be 1.8, of wormwood .7 That is, the camphor dose was raised .3, the wormwood dose lowered 1.3

Histology: The bit of muscle present overlies a greatly degenerated area of brain in which the meningeal relationships are completely lost. The degenerated and partially autolyzed brain tissue is slightly ingrown with connective tissue; the normal brain, however, is practically free of connective tissue if one may judge without serial sections. There is active phagocytosis.

4156.
Histology continued: The sections show an active destructive process with practically no connective tissue reaction. They suggest that the lowered convulsant threshold may be due to a local area of cortical hyperexcitability, and in this cat the convulsive attacks were from the post-operative onset of focal origin with later spread.

4157: Large Tom.
Occipital pole excision:(W.P). Sutures set about the occipital pole, drawn, and block lopped out. Dura sewn satisfactorily.

Date:	Weight:	Dose:	Total:	Result:	Convulsant:	Days:	Remarks.
12/18	3.9 x	1.7:	6.6	(1)			i.p.
2/18	4.0 x	1.7:	6.8	(0)	C.	59	
3/6	4.5 x	1.9:	8.6	(0)		75	
3/11	4.6 x	2.1:	9.7	(0)		80	
3/15	4.6 x	2.3:	10.6	(0)		84	
3/20	4.6 x	2.5:	11.6	(0)		89	
3/27	4.6 x	2.7:	12.5	(0)		96	
4/3	4.5 x	2.9:	13.0	(0)		103	
4/15	4.7 x	3.1:	14.6	(3)		115	bilateral.
4/15	Death in status.						

Summary of Dosing: Pre-operative camphor dose established at 1.7 cc/Kg. The post-operative camphor dose was found to be 3.1. That is an increase of 1.4 The cat died in a camphor convulsion before being dosed with wormwood.

Histology: Study of the sections shows an irregular and uncertain dural covering over the excised surface. The gross findings of relatively little reaction at the excision site were not borne out in that microscopically there could be seen a proliferation of connective tissue over the excision surface, with many fine connective tissue projections at right angles to the surface, penetrating sometimes as deeply as the white matter.

The operative objective was not obtained in this case if one may judge histologically. Confirmation is lacking in the form of results with wormwood oil, but the appearance of the sections is much like that seen in #4135.

4159: Adult male.
Frontal pole excision: (W.P.) Block suture excision of the entire pole anterior to the cruciate sulcus. Dura carefully sewn.

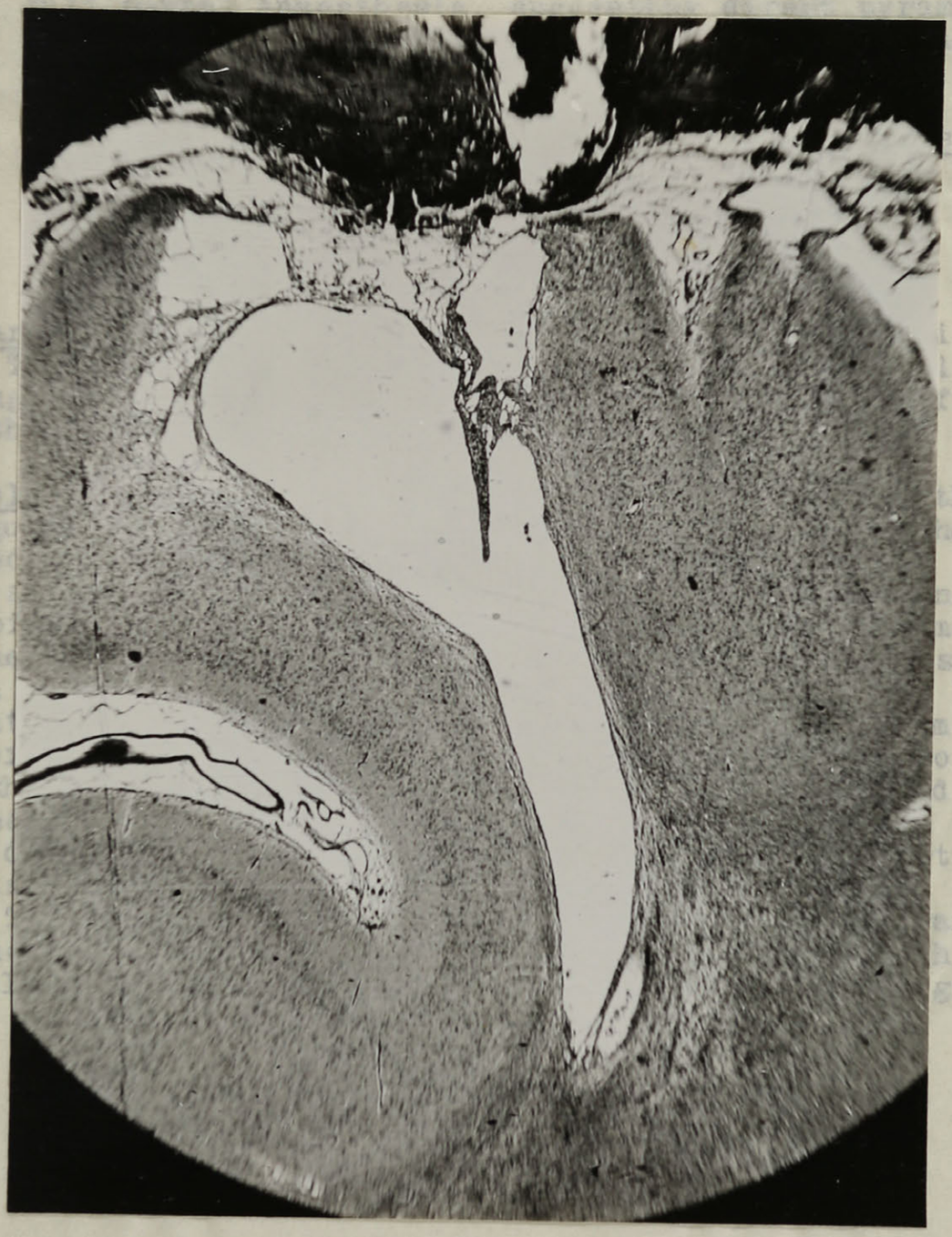
Date:	Weight:	Dose:	Total:	Result:	Convulsant:	Days:	Remarks:
12/20	2.7 x	1.7:	4.6	(2)	C.		i.p.
2/18	3.5 x	1.7:	6.0	(0)		57	
3/6	3.6 x	1.6:	5.8	(0)		73	
3/11	3.5 x	1.9:	6.6	(0)		78	
3/15	3.4 x	2.2:	7.6	(0)		82	
3/20	3.3 x	2.4:	7.9	(0)		87	
3/27	3.4 x	2.6:	9.1	(0)		94	
4/3	3.4 x	2.9:	10.0	(0)		101	
4/15	3.4 x	3.2:	11.0	(0)		113	
4/24	3.3 x	3.4:	11.2	(2)		122	Bilateral with subsequent paresis rt. rear.
4/25				(S)		123	Convulsive movements bilaterally of face.
6/3	3.6 x	2.4:	8.8	(2)		142	
6/12	3.5 x	2.2:	7.8	(0)		151	
6/24	3.0 x	1.0:	3.0	(0)	W.	163	
6/28	3.1 x	1.5:	4.6	(0)		167	
7/18	3.0 x	2.0:	6.0	(0)		187	
7/23	3.0 x	2.4:	7.2	(2)		192	Bilateral.
7/28	3.0 x	2.2:	7.0	(2)plus		197	Not lateralized.
8/1	3.0 x	2.0:	6.0	(0)plus		201	
8/6	Sacrificed.						

Summary of Dosing: Pre-operative camphor dose established at 1.7 cc/Kg The post-operative camphor dose was found to be 2.4, of wormwood 2.1 That is, the camphor dose was raised .7, the wormwood dose was raised .1

Histology: The muscle, throughout which there is a great deal of cellular reaction, has become firmly adherent to the underlying meninges. The dura cannot be made out with definition. The arachnoid has become cystic and there are great interstices where it drops in to fill occasional depressions. The cerebral defect resulting from the excision reaches down into the white matter. It is lined with a single layer of cells, apparently an extension of the pia-arachnoid, supported upon a tangentially running glial framework.

The picture is one of a clean, fluid-filled space lined with a pia-arachnoid extension. While there is appreciable gliosis there is practically no connective tissue reaction. There is relatively little phagocytosis. This is the type of operative result that has been sought in doing the excision operation. (Photograph)

4159, Cat, Excision



An excision followed by no scarring and
no drop in the convulsant threshold.
Note the depth of the cyst.

4182: Large Tom.
Excision of Occipital Pole: (J.P.E) Pole excised cleanly by sharp and blunt dissection, without use of sutures. Temporal fascia transplant necessitated to close dura because of herniation. During the excision the animal jumped suddenly, despite full amytal anaesthesia, suggesting direct pyramidal tract injury. This injury was confirmed by histological study, as will be seen below.

Date:	Weight:	Dose:	Total:	Result:	Convulsant:	Days:	Remarks.
1/24	3.3 x	1.7:	5.6	(2)	C		
4/3	3.2 x	1.7:	5.4	Death in status.		62	

Summary of Dosing: Pre-operative camphor dose established at 1.7 cc/Kg. The post-operative camphor dose was found to be 1.7, that dose giving rise to status epilepticus and death 62 days after operation, and the second time that it was ever dosed.

Histology: Dense meningo-muscular adhesions. Under the dura is an irregularly interrupted arachnoid which at intervals has become displaced to allow reacting cells and degenerating brain tissue to lie in thin sheets between it and the dura. At other portions of the section the pia-arachnoid is absent in long stretches, and damaged cerebral tissue lies directly under the dura. Phagocytosis is marked and there is an extensive accompanying fibrosis and deep in the block there is slight cystic formation. A portion of the brain stem is included and examination proves that there was direct injury to it at operation for there is an ingrowth of meninges filled with blood into a moderately deep cut. Weigert-Pal stains of the cervical and thoracic cord show degeneration in the regions of the rubro-and cortico-spinal tracts on both sides, more marked on the right.

The picture is one of active and progressive brain damage with degeneration, phagocytosis, connective tissue ingrowth, cystic change and slight gliosis. In addition there is tract damage.

Summary of results obtained in operated cats.

1. The post-operative doses of camphor and of wormwood do not correspond.

2. The following tables summarize the changes in doses above or below the normal, and contrast the results obtained with camphor and wormwood.

(A)

Wounds.	Camphor Increase	Wormwood Decrease.	Average Wormwood decrease.
Motor			
4134	.5	1.6	
4136	.8	1.1	
4191	.5	1.4	
4192	0	1.1	1.3
Frontal			
4160	2.0+	1.2	
4167	1.4	1.4	1.3
Occipital			
4179	1.9	.7	
4180	.3	.8	.75

(B)

Excisions.	Camphor Increase.	Wormwood Change.
Parietal		
4103	.3	-1.1
Motor		
4105	.7	+ .3
4135	1.2	-1.2
Frontal		
4156	.3	-1.3
4159	.7	+ .1
Occipital		
4157	1.4	?
4182	?	

3. It can be seen from the above tables that among the wounds the reaction to wormwood was consistent among the three groups, whereas this cannot be said of the reactions to camphor. This we regard as but another evidence of the unreliability of camphor, attention to which we called above. The table indicates further, though the number of cases is far too small to draw definite conclusions, that wounds in the motor area and the frontal area (generally in cats involving the motor area) lower the dose twice as far as wounds in the occipital area.

4. Among the excisions the same irregularity of reaction to camphor can be seen.

5. Only five of the seven animals in this group can be included in the discussion for two died before being dosed with wormwood. Of these five the doses of three decreased, indicating an increased convulsive tendency. Presumably in these cases the operative aim was not attained and a lesion comparable to a brain wound was created.

6. Microscopic study confirms the opinion that the operative aim was not attained. In cats #4135 and #4182 a severe post-operative scarring has occurred as indicated in the protocols. In #4156, a third excision in which the minimum convulsant dose was lowered, there is little scarring. On the other hand, the histological picture in this case was one of an actively destructive lesion such as might well be a locus minoris resistentiae to a direct cortical stimulant, if such be considered the action of wormwood oil and camphor. It is perhaps significant that this cat's attacks were frequently focal in character or focal in onset. #4103, a parietal excision, judging from the lowering of the convulsant threshold, should be classed as a wound. Histological confirmation of this grouping is not available for this animal is being saved for further observation.

7. Invariably when scarring was the operative aim the minimum convulsant dose was lowered as anticipated. In these cases fibrosis of a moderate or marked degree was present in the form of connective tissue ingrowth into the cerebral tissue. In addition there was invariably anchoring of the brain and an arachnitis of varying degree.

Pre-operative Camphor Doses in Monkeys:

The monkeys used in these experiments (macacus rhesus) were acquired at three different times. The first group proved to have minimum convulsant doses quite comparable to those of the usual run of cats. They reacted in uniform fashion to pre-operative dosing with camphor and no controls were kept after it was felt that the doses had been safely established. The second and third groups, obtained from the same dealer and having their origin in India as had the first group, differed from their fellows in having hairless tails. A representative of the company considered them to be closely allied. The minimum convulsant doses in these animals were, however, slightly lower. One animal was kept as a control from the second group and has not been operated upon but has been dosed with camphor at regular intervals. He has shown a remarkable constancy of reaction. His record is given here, the pre-operative doses of the other monkeys being given with the individual protocols.

Camphor Dosage in Control Monkey,

4215:

Date:	Weight:	Dose:	Total:	Result:	Convulsant:	Days:	Remarks.
4/22	2.0 x	1.6:	3.2	(2)////	C.		Bilateral.
4/25	2.0 x	1.2:	2.4	(0)		3.	
4/28	2.0 x	1.4:	2.8	(2)///		6	Bilateral.
5/6	2.3 x	1.2:	2.7	(2)		14	"
5/9	2.0 x	1.0:	2.0	(0)		17	"
5/13	2.0 x	1.2:	2.4	(2)/		21	"
5/19	2.2 x	1.1:	2.5	(0)		27	"
5/27	2.0 x	1.2:	2.4	(1)(1)(2)		35	"
5/30	2.0 x	1.1:	2.2	(0)		38	
6/2	2.0 x	1.2:	2.4	(2)		41	
6/16	2.2 x	1.1:	2.4	(0)		55	
6/27	2.1 x	1.2:	2.5	(2)		66	
7/16	2.0 x	1.1:	2.2	(2)(1)(2)		85	
7/17	Death - miliary tuberculosis.					86	

Comment: The minimum convulsant dose of this animal was established at 1.2 cc/Kg. Dosed with camphor thirteen times he showed no appreciable change at any time. Even the day prior to death from miliary tuberculosis there was little change in his reaction to the convulsant.

Post-operative Doses in Monkeys:

The operated monkeys have been divided into four groups. Group I comprises a single animal, used as an operative control. In his case a simple decompression was done over the motor area, the dura was opened and immediately closed, after which the closure of the skin flap was made in the usual fashion. As will be seen this procedure was without effect on the minimum convulsant dose. This fact having been established, exploratory operation was done, a brain wound made, and the animal was transferred from Group I to Group II. However, he died so shortly after, that he is included only in the first group.

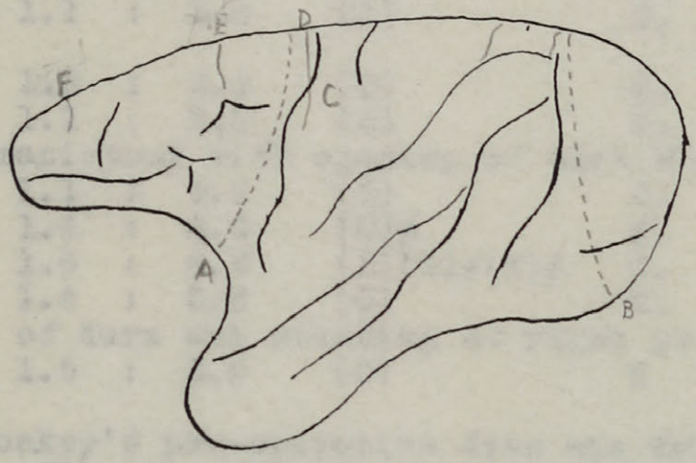
Group II is made up of six animals in which brain wounds were performed. Many of these animals had had unilateral cervical sympathectomies; one had had a bilateral sympathectomy. In these operations the vertebral portions of the inferior cervical ganglion with the nerves running to and on the vertebral artery were taken; occasionally the entire stellate ganglion rather than only the vertebral portion of it was taken. (For a description of the operative procedure of vertebral ganglionectomy, see Geydin and Penfield 1929). In addition the superior cervical ganglion with its branches was dissected out, the branch running to the internal carotid artery avulsed, and finally the internal carotid artery was decorticated as had been the vertebral. In no instance could any change upon the type or severity of the later convulsions be observed other than as listed in the comments in the protocols; therefore all these animals are grouped with those having only brain wounds. Note

is made in each instance, however, when a sympathetic operation had been performed. These animals will be included more fully in a later report bearing upon the vasomotor supply of the cerebral arteries - to be issued from the department.

Group lll comprises four monkeys. In two of these block excision of the pre-precentral region was performed, in the third a frontal pole amputation was done; in the fourth the frontal pole and also the tip of the temporal were amputated. Of these animals two have been kept for further observation.

Group lV includes only two animals, long-standing brain wounds with a definite reduction of minimum convulsant doses in which the cerebral scars were removed in an attempt to raise the minimum convulsant doses back to their old thresholds. Both of these animals are being kept for a longer period of observation.

Surface Markings of the
Brain of Macacus Rhesus



A. Coronal suture, which forms a convenient landmark to the central gyrus which it sometimes overlies.

B. Lamdoidal suture.

C. Central gyrus.

D. Pre-central vein.

E. Posterior frontal vein

F. Anterior frontal vein

Note: The location of the veins is variable, as in the human. The figure represents the usual findings. Faradic stimulation has always been used to locate the motor zone. It may ex- somewhat further forward than indicated.

Group 1: Decompression and Dural Opening.

4240: Female.

Operative Note: Craniotomy with opening of dura, right. J.P.E. After decompression the dura was opened and turned upward exposing the pre-central vein. The flap was immediately returned to place and carefully closed. At the bottom it could not be closely approximated and a gap of 2 mm. was left for a distance of 4 or 5 mm.

Date:	Weight:	Dose:	Total:	Result:	Convulsant:	Days:	Remarks:
5/9	2.8	x 1.5 :	4.2	(2)(0)/	C.		0/ twitchings of both eyelids, 7 on Lt; twitchings of left face.
5/13	2.5	x 1.4 :	3.5	(1)(2)	C.		Bilateral.
5/19	2.5	x 1.2 :	3.0	(2)	C.		"
5/27	2.7	x 1.1 :	3.0	(1)	C.		Not lateralized.
5/30	2.5	x 1.0 :	2.5	(0)	C.		
6/2	2.6	x 1.1 :	2.8	(0)	C.		
6/5	Simple craniotomy with opening of dura right.						
6/27	2.7	x 1.1 :	3.0	(0)	C.	22.	
7/16	2.6	x 1.4 :	3.6	(0)/	C.	41.	
7/22	2.7	x 1.6 :	4.3	(2)(1)/(2)/	C.	47.	
7/25	2.7	x 1.4 :	3.8	(0)	C.	50.	
7/30	Excision of dura and wounding of right pre-precentral area.						
8/11	2.5	x 1.5 :	3.8	(0)	C	67	

Summary: This monkey's pre-operative dose was definitely established at 1.1 cc/Kg. After the operation its minimum convulsant dose rose to 1.5 cc/Kg. Fifty-five days post-operatively the operative site was re-opened. The loose areolar tissue underlying the skin was adherent to the underlying dura but showed no inflammatory changes. The dura in turn was quite adherent to the pia-arachnoid in several places. The dura was excised and with it was taken a small block of adherent cerebral tissue for microscopic examination. A good deal of intentional, but quite superficial, wounding of the brain substance was then done. Dural defect not closed, the remaining fenestrated areolar tissue was drawn over, and the skin tightly closed. Monkey transferred to Group 2. Shortly after transfer, and before the post-operative dose could be re-established it died suddenly of miliary tuberculosis.

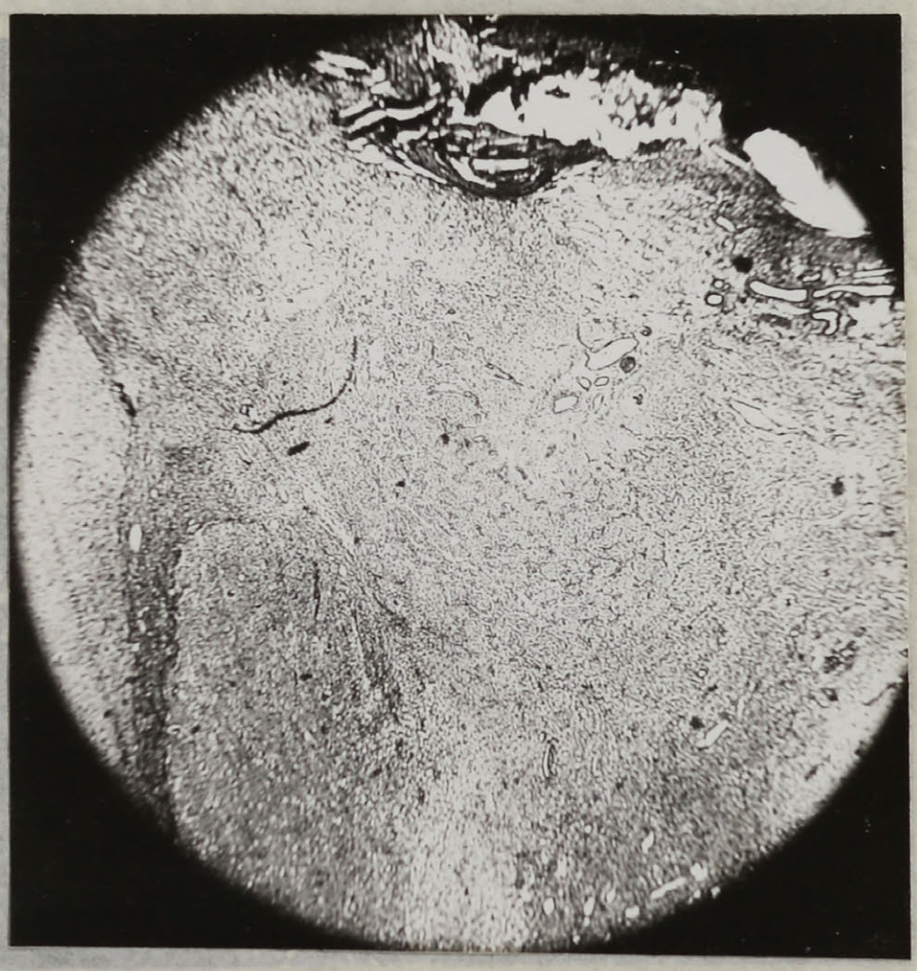
Examination of excised dura and brain: Examination ofthe sections of dura and the immediately adjacent brain which were removed at the second operation, the time of infliction of the brain wound, shows the dura to have become adherent to the overlying areolar tissue and muscle fibers. The dura in turn is adherent to the underlying arachnoid which, however, seems to be no more adherent than usual to the underlying pia. The cerebral tissue shows no connective tissue or glial reaction whatsoever. The end result of the first operation was then, simply an anchoring of the meningeal coverings and therefore of the brain to the extra-cranial tissues. There was no brain damage.

#4240 continued.

Study of the brain wound removed at post-mortem. The dura and reacting arachnoid have become adherent to a large block of degenerating cerebral tissue isolated from the remainder of the brain by two heavy connective tissue partitions passing downward into the cerebral tissue, not joining in the depths but sending out occasional spraying fibers at their deepest parts. Between these two partitions there run through the degenerating brain tremendous numbers of small capillaries breaking up the cerebral tissue into groups of ten, twenty and thirty nuclei. Superficially, where the degeneration seems to have progressed more rapidly, scavenger cells are present in abundance. Deeper, phagocytosis seems not to have begun as yet.

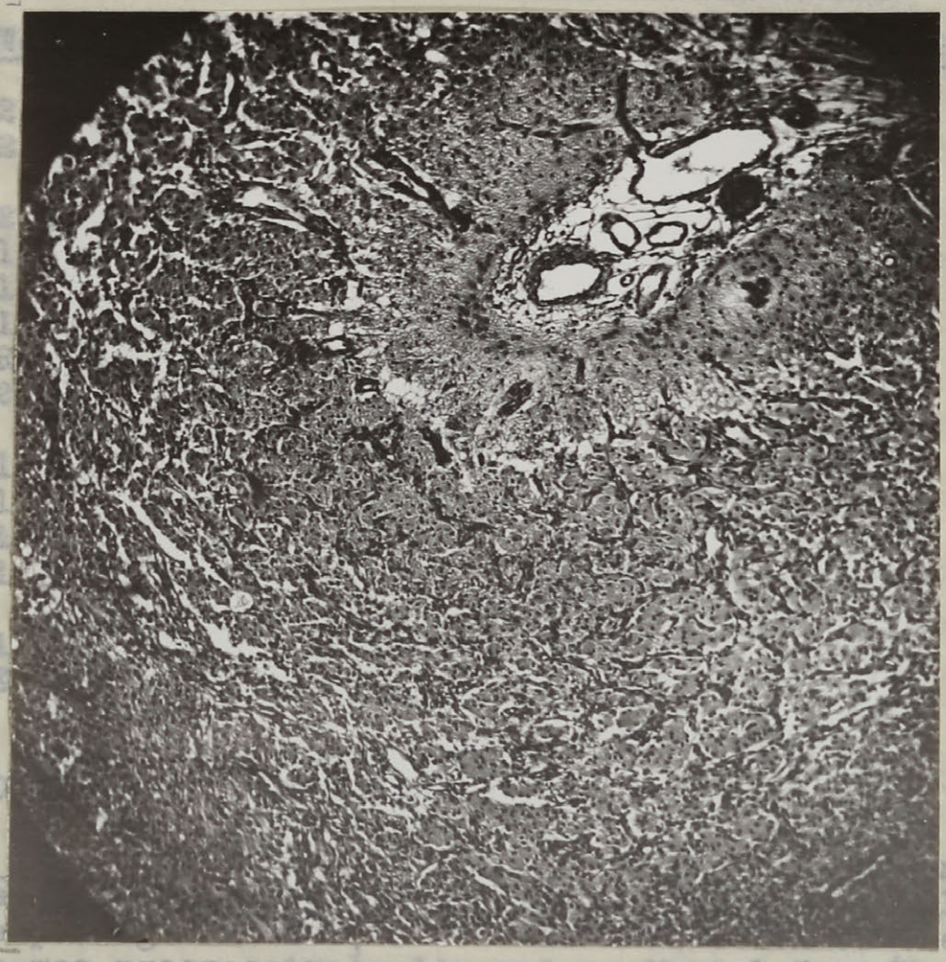
This animal, who died eleven days after her second operation, forms the most striking example of the series of the basis for later cerebral scarring (Photograph).

4240, Monkey, Wound



Low power view of a recent cerebral wound showing the remarkable increase in vascularity and illustrating the isolation of small collections of cells by capillary ingrowth.

4240, Monkey, Wound



A higher magnification of the capillary proliferation shown in the previous plate.

Group 11: Brain Wounds.

4142: Male.

Operative Note: Right pre-precentral region wound. (J.P.E) Motor area defined by faradic stimulation. Anterior to the arm center a block of tissue 1½ x 1½ cm. and about 2 cm. deep was partially excised, so that it hung by a posterior flap. The pia-arachnoid of the surrounding area was damaged. Dura was closed with continuous silk suture.

Superior & Inferior Cervical Ganglionectomy, right. 2/5/30.

Date:	Weight:	Dose:	Total:	Result:	Convulsant.	Days:	Remarks:
1/10	2.0 x	1.5:	3.0	(0)	C.		
1/17	2.2 x	1.6:	3.5				Full dose not given.
1/23	2.0 x	1.6:	3.2	(1)			
2/24	1.8 x	1.6:	2.9	(0)		19	
3/12	1.9 x	1.7:	3.2	(2)		35	Bilateral.
3/18	1.8 x	1.7:	3.1	(2)/		41	
3/21	Right pre-precentral wound.						
4/10	2.2 x	1.6:	3.5	(2)////		20	Lt.sided preponderance.
4/16	1.8 x	1.3:	2.3	(0)		26	
4/22	1.5 x	1.4:	2.1			32	
4/25	1.6 x	1.4:	2.2	(2)		35	Lateralization?
4/28	1.8 x	1.3:	2.3	(2)/////		38	Jacksonian; rt. sided.
5/6	1.6 x	1.0:	1.6	(0)		46	
5/9	Ergotamine 3 mg. by stomach tube					49	
	" ½ / 1 mg. i.v. at half hour intervals.					53	
5/20	Death - miliary tuberculosis.					60	

Summary of Dosing: A pre-operative dose of 1.6 was not varied appreciably by a right superior and inferior cervical sympathectomy. With the passage of time, after the infliction of the brain wound, the dose was progressively lowered so that 1.3 cc/Kg. gave a series of convulsions at 38 days. 1.0 cc/Kg. at 46 days was under the convulsant threshold. Unfortunately the animal died two months post-operatively of miliary tuberculosis.

Histology: There is a dense musculo-meningeal-cerebral adhesion. The arachnoid is greatly proliferated throughout the entire section and is infiltrated with many scavenger cells. A broad connective tissue core extends down to the white matter. The picture is one of a typical wound reaction.

4143: Male.

Pre-precentral Brain wound, right. 2/13. J.P.E.
By faradic stimulation the hand and foot areas were located and anterior to them several deep cuts were made into the cortex nearly isolating a block of tissue. The area wounded lay directly under the pre-central vein which was tied on either side of the area. When the dura was turned back it was punctured several times with a dural hook in the hope of promoting adhesions. The dura was closed completely except for a small gap anteriorly.

Date:	Weight:	Dose:	Total:	Result:	Convulsant:	Days:	Remarks
1/10	2.0	x 1.5	: 3.0	(0)	C		
1/17	2.3	x 1.6	: 3.7	(0)			
1/23	2.5	x 1.7	: 4.2	(0)			
2/ 4	2.2	x 1.8	: 4.0	(2)			
3/12	2.0	x 1.8	: 3.6	(2)(lt?)(2) (2)(rt)		40	Rt. sided jerking.
3/18	2.0	x 1.7	: 3.4	(2)		46	Not lateralized
3/25	1.9	x 1.7	: 3.2	(0)		53	Jerking of rt. foot
3/25							Bitten by rats
4/ 4	Convulsive seizure of left face - no involvement of extremities					63	
4/ 5	Death - miliary tuberculosis					64	

Summary of Dosing: This protocol serves to demonstrate that the reduction of dose following operation varies in different animals. Whereas in the previous animal there was a definite reduction in dose at 38 days, in this one there had been no appreciable reduction at 53 days. On the 63rd day, however, the day prior to death, there was observed a definite Jacksonian convulsion of short duration involving the left face. Apparently the miliary tuberculosis was a much better "convulsant" than was the camphor.

Histology: The gross specimen shows the overlying skin and areolar tissue to be adherent to the dura. The dura in turn is adherent to the brain. Microscopically the dura is found not to be vascularized and the pia-arachnoid, except in the immediate vicinity of the wound, is normal.

A tongue of brain tissue, that nearly isolated at the time of operation and now completely degenerated, is in the section completely isolated from the remainder of the brain by connective tissue septa, made up of a loosely proliferated arachnoid extension filled with scavenger cells. At the base of the tongue the connective tissue extends onward into the brain sending in numerous projections, not highly vascularized but accompanied by great numbers of scavenger cells. There is a slight glial reaction. The possibility of connective tissue pull in this instance was great, apparently.

4139: Male.

Operative Note: Right Motor Cortex Wound. 4/11/30. J.P.E.
A very extensive wound of the motor cortex involving the hand and foot areas as outlined by faradic stimulation was made. It was not deep, however, extending only about 5 mm. into the motor cortex. The dura was closed anteriorly, but that portion of it overlying the wound was shredded.

Date:	Weight:	Dose:	Total:	Result:	Convul-sant:	Days	Remarks
12/12	2.3	x 1.7 :	3.9	(2)(1)(2)/	C		i.p.
1/10	2.0	x 1.5 :	3.0	(0)			
1/17	2.0	x 1.5 :	3.0	(0)			
1.23	1.9	x 1.6 :	3.0	(0)			
2/ 4	1.9	x 1.7 :	3.2	(0)			
2/14	2.0	x 1.7 :	3.4	(1)			
2/20	1.9	x 2.1 :	4.0	(0)	W		
2/24	1.9	x 2.6 :	4.9	(0)	W		
3/12	2.0	x 10.0 :	20.0	(0)	W		
3/18	2.0	x 1.7 :	3.4	(2)//	C		
3/25	4½lb	x .2cc :	.9cc	(0)	Ess.of A		
3/28	4lb6oz	x.35cc :	1.5cc	(0)	Ess.of A		
4/28	1.8	x 1.5 :	2.7	(1)	C	17	Not lateralized
5/ 6	1.9	x 1.3 :	2.5	(1/)		25	" "
5/ 9	1.9	x 1.0 :	1.9	(0)		28	
5/13	1.76	x 1.0 :	1.76cc	(0)		32	
5/27	1.9	x 1.0 :	1.9	(0)		46	
6/16	2.0	x 1.1 :	2.2	(0)		66	
7/ 2	Death - Tuberculosis.						

Summary of Dosing:- In this animal, a wound situated directly in the motor area, reduced the dose of camphor only from 1.7 to 1.3 at 25 days. At 66 days 1.1 did not produce a convulsion. Unfortunately this animal's life was also cut short by severe tuberculosis.

Histology: At post-mortem the dura was torn away from the underlying brain to which it was adherent and connection was maintained only by two large capillaries running from dura into the wound site. In preparation of the microscopic section the dura was completely lost. Examination of the sections microscopically shows a cerebral defect of about 3 mm. depth which is lined by a pia-arachnoid extension. From the bottom of the defect extends just into the white matter a wound track the lower half of which is filled with a connective tissue core from which there extend outwards glial fibers. The gliosis is only moderate and there is a good deal of cystic change about the track itself. Near the surface of the brain the track is empty except for the presence of three large capillaries. At the surface of the brain there are a great many red blood cells and occasional phagocytes. The walls of the track down to the connective tissue core are lined with many red blood corpuscles and occasional phagocytes.

4149: Male.

Operative Note: Right Motor Cortex Wound. J.P.E.
Faradic stimulation of the supposed motor cortex resulted only in movements of the arm. This active area, lying behind the pre-central vein, was almost isolated with scissors cuts. Dura closed completely.

Superior & Inferior Cervical Ganglionectomy, right. 2/5.

Date:	Weight:	Dose:	Total:	Result:	Convulsant:	Days:	Remarks:
1/17	2.6 x	1.6 :	4.2	(2)	C		
1/23	2.6 x	1.6 :	4.2	(2)			
2/24	2.4 x	1.6 :	3.8	(0)		19	
3/12	2.5 x	1.7 :	4.2	(3)(2)		35	Bilateral
3/18	2.4 x	1.7 :	4.1	(2)ŕŕŕŕ		41	"
3/19	Right Motor Area Wound.						
4/10	2.5 x	1.6 :	3.7	(2)ŕŕŕŕŕ	C	22	Predominantly rt. sided, some little lt. sided twitchings.
4/16	2.4 x	1.3 :	3.1	(3)(2)ŕŕ		28	Rt. sided twitchings
4/22	2.5 x	1.1 :	2.7	(2)		34	" " "
4/25	2.7 x	1.0 :	2.7	(2)		37	" " "
4/28	2.4 x	0.8 :	1.9	(0)		40	
5/ 6	2.5 x	0.7 :	1.7	(0)		48	
5/ 4	2.5 x	.76 :	1.9	(0)		51	
5/13	2.5 x	.8 :	2.0	(0)		55	Full dose not given
5/27	2.6 x	.8 :	2.0	(0)		69	
6/27	2.9 x	.8 :	2.3	(0)		100	
7/16	2.8 x	.9 :	2.5	(2)		119	Not lateralized
7/22	2.7 x	.9 :	2.4	(0)		125	
7/25	2.9 x	.9 :	2.6	(0)		128	
7/30	2.8 x	.9 :	2.5	(0)		133	
8/11	Not dosed.						

Summary: The change in this animal's dosage following sympathectomy is difficult to account for. Maximum functional disability of the sympathetic on the right side presumably occurred before 19 days so that it seems hardly likely that the sympathectomy was responsible for the change. The possibility of an increasing susceptibility to camphor which is only aggravated in the dosages following the cerebral injury must be considered. Certainly it is strongly suggested. Our interpretation, perhaps prejudiced, would be that the large number of convulsions on the forty-first day after sympathectomy was more or less of a chance happening, that 1.6cc/Kg or 1.5 would have been the minimum convulsant dose, a not significant change. The drop in the minimum convulsant dose from the pre-operative 1.6 to 1.0 on the fortieth day post-operatively is, then, striking. Repeated attempts through the 133rd day failed to lower the dose any further.

4145: Male.

Operative Note: Bilateral Motor Cortex Wounds, hand areas. 4/11 Motor areas outlined by faradic stimulation. Bilateral wounds of the hand areas - three cornered blocks of tissue several mm. in diameter, and several mm. deep were nearly excised. Subsequently the overlying pia-arachnoid was scarified. Dura completely closed bilaterally.

Date:	Weight:	Dose:	Total:	Result:	Convulsant	Days:	Remarks:
1/10	3.2	x 3.2	: 5.1	(2)	C		
1/23	3.0	x 1.6	: 4.8	(2)/			
2/ 4	3.0	x 1.5	: 4.5	(0)			Full dose not given 1.4cc
2/ 8	2.9	x 1.5	: 4.3	(2)(2)			
2/20	2.9	x 2.4	: 7.0	(0)	"		
2/24	2.9	x 3.2	: 9.3	(0)	"		
3/12	2.9	x 4.5	: 13.0	(0)	W		
3/18	2.7	x 11.0	: 29.5	(0)	"		
3/25	6lb4oz	x .04cc	: .25cc	(0)	Ess.of A		
3/28	6lb5oz	x .25cc	: 1.6cc	(0)	"		
4/28	2.6	x 1.5	: 3.9	(0)	C	17	
5/ 6	2.5	x 1.2	: 3.0	(2)		25	
5/ 9	2.5	x 1.0	: 2.5	(2)		28	Bilateral. Rt. sided jerks slightly exaggerated over it.
5/13	2.6	x 0.7	: 1.8	(2)		32	Bilateral
5/27	2.6	x 0.5	: 1.3	(0)		46	
6/ 9	2.7	x 0.5	: 1.4	(0)		59	
6/16	2.6	x 0.5	: 1.3	(0)		66	
6/18	Right Superior & Inferior Cervical Ganglionectomies . Transection of Right Internal Carotid Artery.						
6/27	2.9	x 0.8	: 2.3	(0)		11	
7/16	2.7	x 1.0	: 2.7	(0)		30	
7/22	2.7	x 1.3	: 3.5	(2)//		36	
7/25	2.7	x 1.1	: 3.0	(0)		39	
7/30	2.8	x 1.2	: 3.4	(2)/		44	
8/4	2.6	x 1.1	: 2.9	(2)//		49	
8/11	2.7	x 0.8	: 2.2	(0)†		56	

Summary of Dosing: Pre-operatively this monkey's dose was established at 1.5 cc/Kg. 32 days following operation the dose had fallen to .7cc/Kg. Three later attempts to establish the dose at .5 cc/Kg failed, the last at 66 days. Why the dose should have increased again after right sided sympathectomy need not concern us here since there is no ground for assuming that the animal has gained a tolerance for the drug through repeated dosing.

4212: Male.

Operative Note: Right Motor Area wound. J.P.E.
The operative procedure followed in this animal differed from that in the other wound monkeys in that in this case a bone flap was turned down instead of a decompression being done. With faradic current the hand and arm areas were located. In the hand area several scissors cuts a centimeter deep were made. The dura was then carefully sewn posteriorly. Anteriorly, over the wounded area, it was shredded. Bone flap carefully replaced.

Date:	Weight:	Dose:	Total:	Result:	Convulsant:	Days:	Remarks:
4/16	5lb 11ozx	.04	: .22cc	(1)	~~Ecs-ef~~ A		
4/22	2.5	x 1.6	: 4.0	(2)+++++	C		
4/25	2.5	x 1.2	: 3.0	(3)			
4/28	2.5	x 1.0	: 2.5	(0)			
4/30	Operation - Right Superior & Inferior Ganglionectomies. Left Inferior Ganglionectomy.						
5/ 8	Operation - Left Superior Ganglionectomy						
5/27	2.2	x 1.2	: 2.6	(2)(1)(2)+++	Amytal		19
5/30	2.6	x 0.8	: 2.0	(0)	C		22
6/ 2	2.0	x 1.0	: 2.0	(3)			25
6/ 9	2.0	x 0.9	: 1.8	(0)			32
6/16	2.2	x 1.0	: 2.2	(0)			39
6/17	Right pre-central wound						
6/27	2.6	x 1.0	: 2.6	(2)			11
7/16	2.2	x 0.8	: 1.7	(0)			30
7/22	2.3	x 0.8	: 1.8	(0)			36
7/25	Not dosed.						
7/30	2.4	x 0.8	: 1.9	(0)			41
8/11	2.3	x 0.9	: 2.1	(0)			53

Summary of Dosing: The pre-operative dose of 1.2 was little reduced by bilateral cervical sympathectomy. Nor was the dose appreciably decreased by infliction of a brain wound in the motor area. The result suggests that possibly the development of convulsion was prevented by the sympathectomy. This and other results of sympathectomy need not be discussed here.

Group III: Excisions.

4213: Male.

Operative Note: Excision of Right Frontal Pole and of Tip of Right Temporal Pole. J.P.E.

Bone flap. Dura turned up so as to expose the entire area anterior to the pre-central vein. Just anterior to the vein movements of the extremities were obtained by faradic stimulation. The line of frontal pole excision lay just anterior to the pre-precantral vein. The removal was clean except for the tissue lying about the origin of the middle cerebral artery. Subsequently the tip of the temporal pole was excised, approach being made behind the great sphenoid wing. Dura tightly closed. Bone flap secured. Two bone buttons replaced.

Date:	Weight:	Dose:	Total:	Result:	Convulsant:	Days:	Remarks:
4/16	4lb 15oz	x 0.07	: 0.34	(0)	~~Essof~~ A		
4/22	2.3	x 3.0	: 6.9	(2)(2)(2) (~~error~~)	C A		Bilateral
4/25	2.3	x 1.3	: 3.0	(0)	C		
4/28	2.0	x 1.4	: 2.8	(0)			
5/ 6	2.1	x 1.5	: 3.1	(2)			Bilateral
5/9	2.0	x 1.4	: 2.8	(1)			"
5/13	2.0	x 1.3	: 2.6	(1)(2)			"
5/19	2.2	x 1.2	: 2.6	(2)			"
5/27	2.3	x 1.0	: 2.3	(2)			"
5/30	2.2	x 0.8	: 1.76	(0)			
6/ 2	2.1	x 1.0	: 2.1	(0)			
6/ 6	Frontal pole excision right and excision of tip of temporal pole rt.						
6/27	2.2	x 1.0	: 2.2	(0)		22	
7/16	2.2	x 1.2	: 2.6	(0)		41	
7/22	2.3	x 1.4	: 3.2	(2)++		47	
7/25	2.3	x 1.2	: 2.8	(0)		50	
7/30	2.3	x 1.3	: 3.0	(0)		55	Left sided paresis.
8/ 4	2.2	x 1.4	: 3.1	(2)++		60	
8/11	2.2	x 1.2	: 2.6	(2)+		67	Second attack right sided, first not lateralized definitely.

Summary of Dosing: A pre-operative dose of 1.0 cc was not lowered by the excision within a period of 67 days. It is too early to say definitely that the dose may not be lowered later. The animal is being kept for further observation.

4233: Male.

Operative Note: Right pre-precentral Area excision . J.P.E. Bone flap. When the dural flap was turned upward an irregular venous distribution was found which led to some uncertainty as to area exposed. With faradic current, however, movements of the extremities were obtained and a block excision of the area lying anterior to the motor area was done. "Four sutures set and tied. A block of tissue 2½ x 1½ x 1½ cm. removed from the mid-line outward... There were a few shreds of white matter left in the bottom of the excavation. The posterior lip was a little ragged." Dura tightly closed. Bone flap secured in place.

Date:	Weight:	Dose:	Total:	Result:	Convulsant:	Days:	Remarks:
5/ 9	3.0	x 1.5 :	4.5	(2)	C		Bilateral
5/13	3.2	given IJ		(3/)	Ol.Abs.		" i.v.
5/19	2.95	.5cc		(1)(2)(2)	" "(1in20)		*Forcible turning of head and eyes to right otherwise bilateral.
5/27	3.7	.2cc		(0)	" "(1in20)		
5.30	3.5	x 1.4 :	4.9	(1)	C		Not lateralized
6/ 2	3.0	.23		(0)	Ol.Abs(1in20)		
6/ 9	3.1	.30		(0)	" "(1in20)		
6/11	Right pre-precentral excision.						
6/27	3.6	x 1.4 :	5.1	(0)	C	16	
7/16	3.3	x 1.5 :	5.0	(0)		35	
7/22	3.1	x 2.0 :	6.3	(2)		41	
7/25	3.0	x 1.7 :	5.1	(0)		44	
7/30	3.0	x 1.9 :	5.7	(0)		49	
8/4	3.0	x 2.0 :	6.0	(2)++		54	
8/11	3.0	x 1.8 :	5.4	(2)+++		61	Not definitely lateralized, probably rt. sided.

Summary of Dosing: A pre-operative dose of 1.4 was raised to 2.0 at 54 days. A week later 1.8 was slightly over the minimum convulsant dose. Whether the dose will drop progressively is a matter of conjecture. The animal is being kept for further observation.

4232: Male.

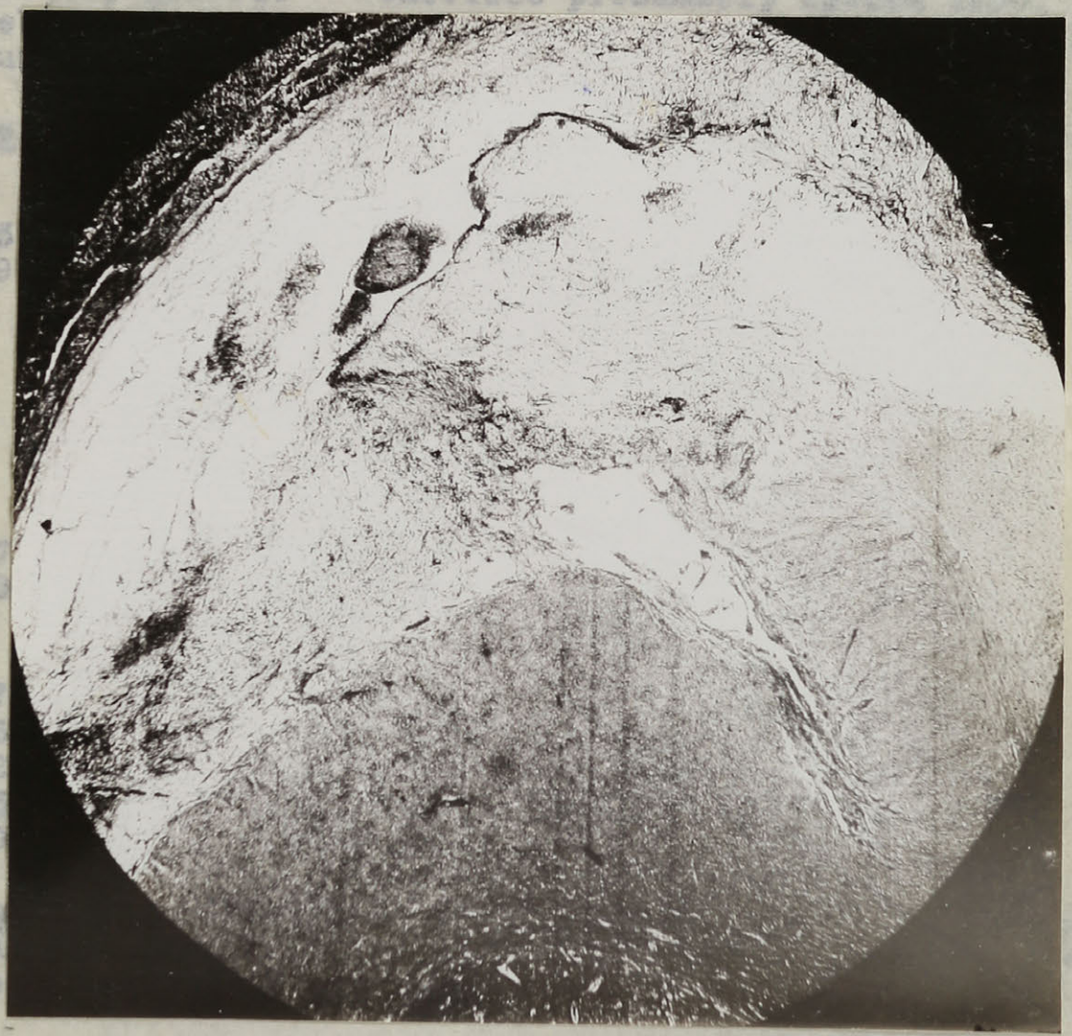
Operative Note: Right pre-precentral area excision . J.P.E. Bone flap. Dura turned upward. Precentral vein exposed in posterior third of exposed brain. With faradic current the motor area was outlined lying behind the vein. Sutures were then set, the posterior one just anterior to the precentral vein, the anterior suture so as to include the pre-precentral or posterior frontal vein. A block of tissue $\frac{3}{4}$" x $\frac{1}{2}$" x $\frac{1}{2}$" cleanly removed. Dura carefully sewn. Bone flap secured in place.

Date:	Weight:	Dose:	Total:	Result:	Convulsant:	Days:	Remarks:
5/ 9	2.6	x 1.5	: 3.9	(2)++(1)	C		Bilateral
5/13	2.4	x 1.2	: 2.9	(0)			
5/19	2.5	x 1.3	: 2.2	(0)			Weakness & incoordination more marked on left.
5/27	2.5	x 1.3	: 3.2	(1)(1)			Bilateral
5/30	Right pre-precentral Excision.						
6/25	Death - cause undetermined.						

Death: 26 days post-operatively and before being redosed, Cause of the death undetermined. The operative wound had healed well. The bone flap was remarkably solid, the cut edges having become firm and united with fibrous tissue. The dural edges had knit well except at each end of the cut where there were small gaps still present. The dura had become adherent to the excision edges.

Histology: The excision surface is covered with a loosely proliferated arachnoidal tissue which likewise fills the narrow space between dura and brain. Throughout the arachnoidal mesh are scattered large numbers of scavenger cells. The vascular reaction is, however, slight and there is practically no connective tissue ingrowth into the cerebral tissue. The process is still early, however, and it is conceivable that with the passage of time connective tissue infiltration might take place. (Photograph).

4232, Monkey, Excision



Minimal saarring reaction following a block excision of cerebral substance from the pre-pre-central area.

4241. Male:

Operative Note: Excision of Right Frontal Pole. J.P.E. Bone flap. Dura turned up exposing the pre-precentral and frontal veins. Faradic stimulation above the fissure of Sylvius gave erratic responses that apparently were due to spread of the current backwards to the motor area. The tip of the frontal pole, all that portion of it lying anterior to the frontal vein, was separated by sharp dissection and removed. No suture material used. The removal was clean except for a few tabs of tissue left in the olfactory groove. Ventricle presumably opened into, though no cerebro-spinal fluid was seen. Dura tightly closed. Bone flap secured.

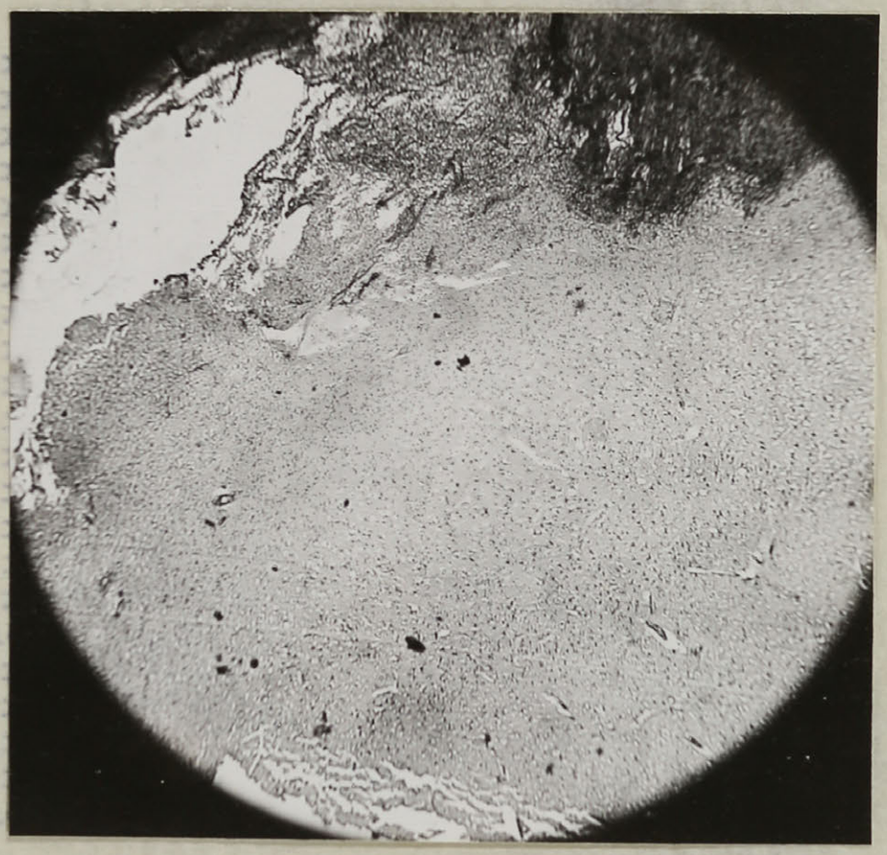
Date:	Weight:	Dose:	Total:	Result:	Convulsant:	Days:	Remarks:
5/9	3.0 x	1.5:	4.5	(0)	C		
5/13	3.1 x	1.6:	5.0	(2)			Bilateral.
5/19	3.1 x	1.5:	4.6	(2)(2)			Bilateral. Inco-ordinate movements & occasional cortical discharges to individual muscle groups.
5/27	2.9 x	1.4:	4.0	(2)			Bilateral.
5/30	3.0 x	1.2:	3.6	(0)			
6/2	3.0 x	1.3:	3.9	(2)(2)(3)			
6/9	Rt. frontal pole excision.						
6/27	3.1 x	1.3:	4.0	(2)		18	
7/16	2.6 x	1.2:	3.1	(0)		37	
7/22	2.7 x	1.3:	3.5	(0)		43	
7/25	2.7 x	1.3:	3.5	(0)		46	
7/30	Death - miliary tuberculosis.						

Summary of Dosing: The pre-operative dose of 1.2 was not altered within 46 days. At the end of that time the monkey died of miliary tuberculosis.

Histology: The excision surface is covered directly by dura, the pia-arachnoid on one side being lost, on the other side becoming fused with the dura as the latter structure reaches the excision site.

Through half the section the dural fibers are arranged parallel to the excision surface; in the other half the dural fibers run at right angles to the brain and there is a slight degree of connective tissue infiltration of the cerebral matter, but relatively little. On one margin there is, at the union of dura and brain, a cellular reaction made up of round cells, a large number of which are loaded with debris. Through this area there is a moderate degree of increased vascularity but the reaction does not extend beyond the excision surface. (Photograph).

4241, Monkey, Amputation of Frontal Pole



Demonstration of the minimal reaction occuring between excision surface and meninges following amputation of a frontal pole.

Group IV: Excisions of Old Brain Wounds.

4146: Male.

Operative Note: Right pre-precentral region wound. 1/27/30. W.P. Parietal decompression. Motor area defined by faradic stimulati on Anterior to the hand area and the pre-central vein several deep scissors cuts were made into the brain substance, almost excising a large block of tissue. Dura satisfactorily closed.

Date:	Weight:	Dose:	Total:	Result:	Convul-sant:	Days:	Remarks:
1/10	2.0	x 1.5	: 3.0	(1)	C		
1/23	1.9	x 1.5	: 2.9	(0)			
2/24	1.8	x 1.5	: 2.7	(1)ff		28	
3/12	1.9	x 1.5	: 2.8	(2)f		44	Right sided
3/18	1.8	x 1.4	: 2.5	(2)f		50	" "
3/25	1.7	x 1.3	: 2.2	(-2)(-2)(1)		57	" "
4/10	1.5	x 1.2	: 1.8	(3)		73	" "
4/16	1.6	x 1.0	: 1.6	(2f)		79	" "
4/22	1.5	x 0.8	: 1.2	(2)		85	" "
4/25	1.5	x 0.7	: 1.0	(0)		88	
4/28	1.5	x 0.8	: 1.2	(0f)		91	
5/ 6	1.5	x 0.6	: 0.9	(0)		99	
5/ 9	1.6	x 0.8	: 1.3	(2)f		102	Right sided
5/13	1.5	x 1.3	: 2.0	(1)(2)ffff(1)		106	" "
5/27	1.5	x 0.5	: .75	(0)		120	
6/16	1.9	x 0.6	: 1.1	(0)		140	
6/23	Excision of Scar right Pre-central region.						
7/16	2.0	x 1.3	: 2.6	(2)fff		23	
7/22	1.9	x 1.0	: 1.9	(2)(1)f		29	
7/25	2.0	x 0.8	: 1.6	(2)		32	
7/30	2.0	x 0.7	: 1.4	(2)		37	
7/31	Excision of Scar.						

Summary of Post-operative Dosing: A pre-operative dose of 1.5 was reduced at 102 days to 0.8. At 140 days there resulted no convulsion on a dose of 0.6.

Operative Note: Excision of Scar, right pre-precentral region. J.P. 6/23/30. The old skin flap was turned down again. The sub-cutaneous tissues were found to be adherent to the dura, with no sign of an old inflammatory reaction. Dura firmly adherent to the bone edges. It was dissected away and the decompression enlarged for better exposure The dura was very firmly adherent to the underlying brain which had become slightly cystic. Increased vascularity of the scar was not present and the cut edges of the isolated dura were not observed to bleed. A slightly stronger faradic stimulus was required to elicit movements from the motor zone than at the first operation though the

current was not accurately enough measured in either operation to draw definite conclusions. Though movements were elicited this time from the scar region no convulsion could be elicited - which may mean that the scar region had not become a true epileptic center. A block dissection with sutures was made of the scar region, apparently in toto. The base of the excision site was left a little ragged. The lateral ventricle was opened into. The operative field was dry at closure. The dural defect was closed with temporal fascia from a healthy cat.

Summary of Post-excision Dosing: By 37 days it was quite obvious that the excision had been without therapeutic effect. Therefore a second excision was planned.

Operative Note: Excision of frontal pole and of pre-precentral region, right. 7/31/30/ J.F.F.
When the old skin flap was again turned down the subcutaneous tissue was found to be slightly adherent to the dural transplant. This had become adherent to the underlying brain, chiefly at the excision edges. At the margins of the transplant there were fine dural-arachnoidal adhesions rather than the dense adhesions more centrally. At the midline the brain about the excision area had become quite adherent to the falx. With faradic stimulus no convulsive movements could be elicited. Thereafter sutures were set just in advance of the motor area and including the pre-central vein. All of the cerebral tissue anterior, to the depth of the lateral ventricle, was excised, including the frontal pole. The temporal pole was not disturbed. The scarred area was probably completely removed, though possibly the excision should have been carried deep enough to enter into the lateral ventricle ~~at~~ in this region.

Subsequent Course: 12 days post-operatively this animal was given 1.5 cc/Kg. There ensued a series of convulsions and the monkey was finally given amytal for protection. While it might be said that there still persisted post-operative irritation and that the convulsions were not the result of scarring, the striking fact is that on two occasions the removal of a scarred area failed to have any effect in raising the convulsant threshold which had presumably been lowered by the scarring.

Histology: Examination of the scar tissue created at the first operation and removed at the second: There is the usual musculo-meningeal-cerebral adhesion which follows wounding. A block of degenerated cerebral tissue is isolated from the remainder of the brain by a connective tissue partition which, shaped like a "Y", contains the degenerated brain in its arms and sends its stem down toward the white matter. The partition contains in its many branched connective tissue fibers abundant phagocytic cells which diminish in number in the stem, finally giving way only to connective tissue fibers which gradually diminish in numbers and finally end before the white matter is reached. It is obvious that the operative procedure removed all the scar tissue created at the first operation (Photograph).

Histology of #4146 continued: Examination of the tissue removed at the third operation, that is, at the second excision: The fascial transplant exhibits a moderate degree of cellular reaction which is made up superficially of polymorphonuclear cells in large part. (There was no clinical evidence of infection post-operatively.) Deeper, however, the reaction changes over to a phagocytosis.

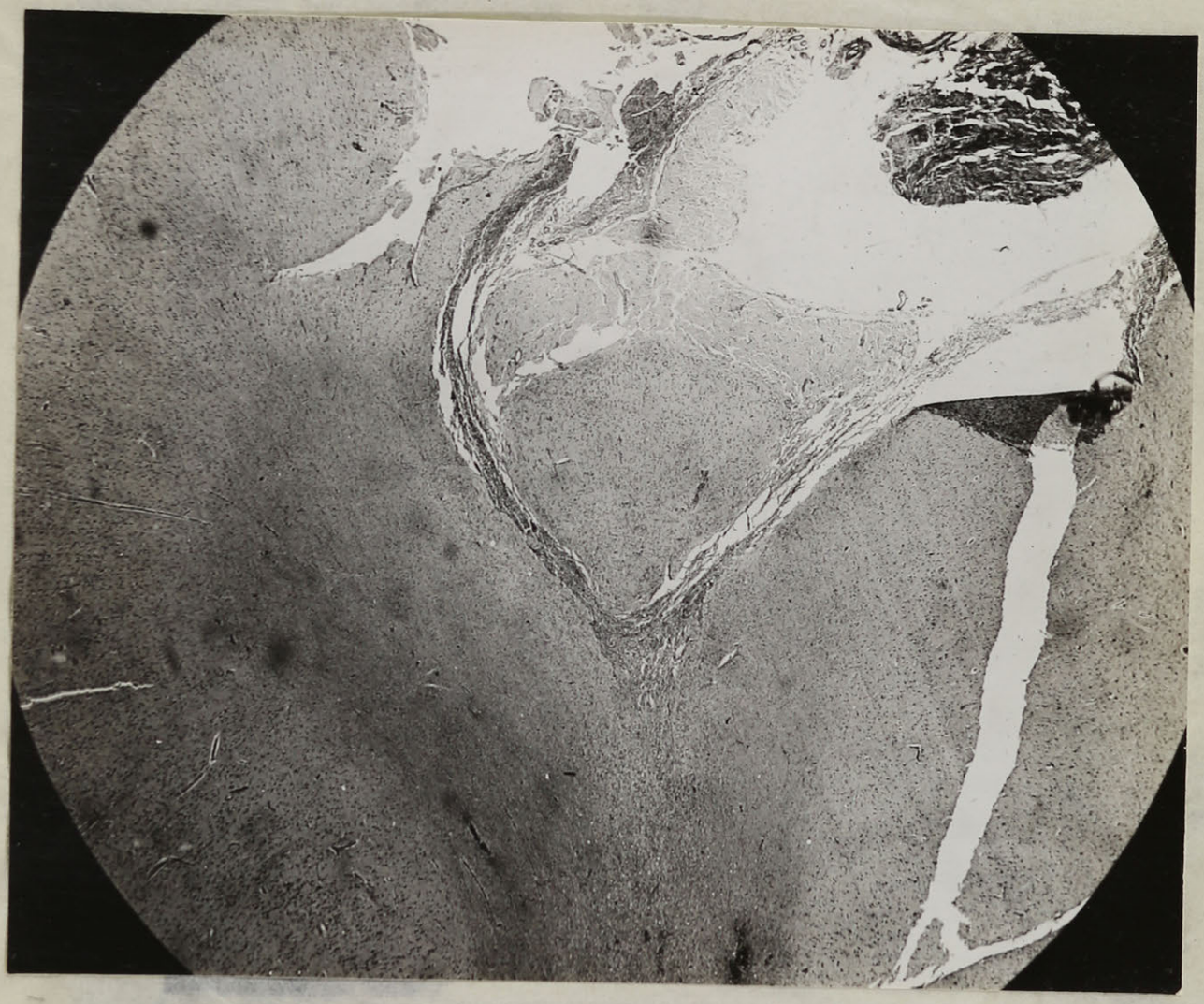
The arachnoid space and excision site is filled with an exuberant connective tissue growth containing in its meshes great numbers of loaded macrophages. There is extensive connective tissue ingrowth into the underlying cerebral tissue.

It is evident from the section that the excision procedure of the second operation was followed by a good deal of reaction and scarring. Further, it is obvious that some of the scar tissue created unintentionally at the second operation was not removed at the third. Therefore this animal continued to carry a cerebral scar which was presumably the reason for the continuance of the low convulsant threshold. (Photograph).

Examination of the brain post-mortem: Thirteen days post-operatively there was found a gaping hole which looked into the excision site. The wound appeared to be clean and there was no sign of inflammation. Presumably the wound opened because of insufficient blood supply to the flap, though a sub-acute infection must be considered as a possibility. Twenty-four hours later severe infection had developed and the brain herniated through the opening. The animal died about twelve hours later.

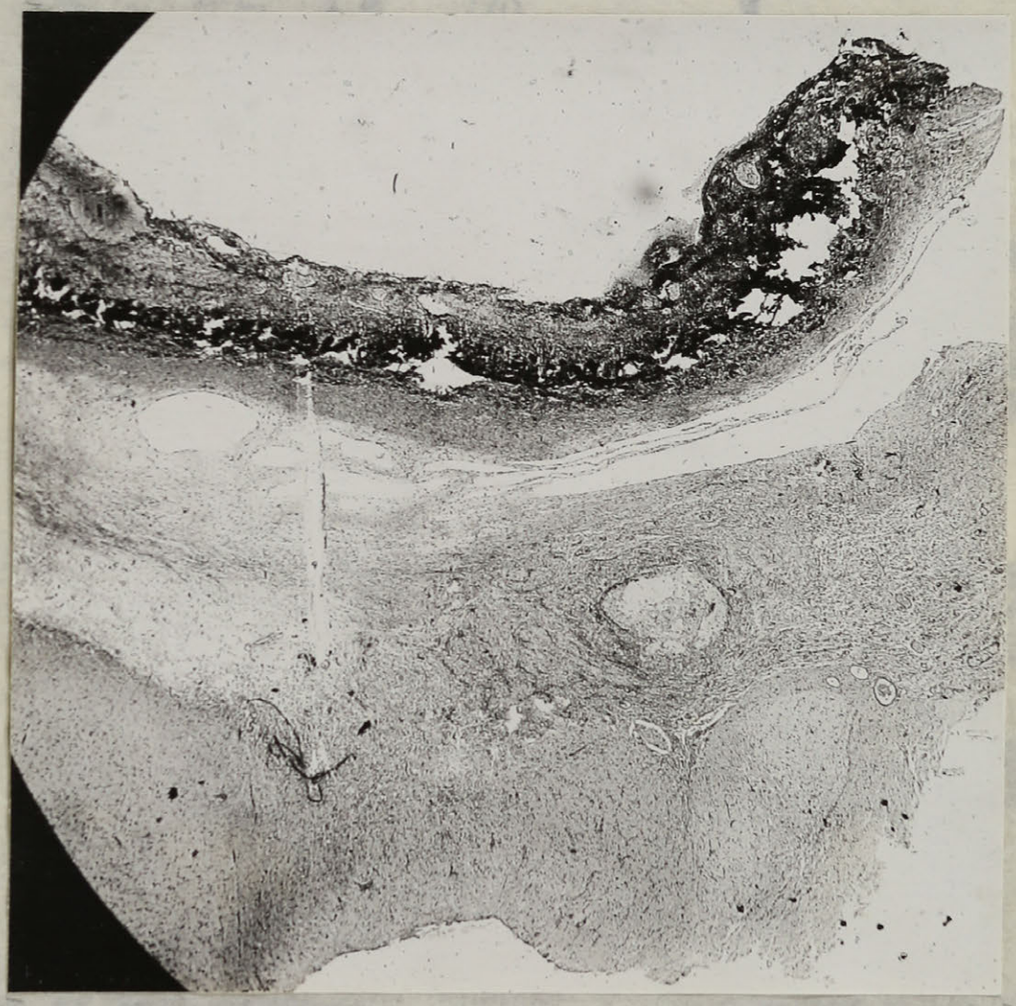
Gross examination of the brain showed an excision site whose topography was so distorted by infection as to make a report of the histology valueless.

4146, Monkey, Wound, Later Excision of Scar



The operative scar removed at the first excision

4146, Monkey, Wound, Later Excision of Scar



A general view of the excision site resulting from the first operative attempt to raise to normal the depressed convulsant threshold. Note the extensive post-operative scarring which signalizes the failure of the operative intervention. (The excised scar is shown in the previous plate.)

4148: Male.

Operative Note: Right Motor Region Wound. 4/4/30.J.P.E. Parietal decompression. With faradic stimulation the hand center was located and several deep scissors cuts were made, the wound being limited to the hand area so far as possible. Dura securely closed over the wound.

Date:	Weight:	Dose:	Total:	Result:	Convulsant:	Days:	Remarks:
10/17	2.2 x	1.6:	3.5	(0)	C		
10/23	2.4 x	1.7:	4.0	(0)			
2/[illegible]	2.4 x	1.8:	4.3	(3/)			
2/20	2.4 x	2.2:	5.3	(0)	W		
2/24	2.2 x	2.7:	6.0	(0)			
3/12	2.1 x	7.0:	14.7	(0)			
3/18	2.1 x	2.3:	4.9	(3)(2)//(3)	C		
3/25	51b/ x	.15cc.					
		/1.5cc.	2.2	(0)	Ess.of A.		
3/28	51b.2oz.x	.4cc:	2.0	(0)	Ess.of A.		
4/22	2.0 x	1.8:	3.6	(2)/	C	18	Not lateralized
4/25	2.3 x	?	2.4?	(0)		21	
4/28	2.0 x	1.6:	3.2	(3)(2)		24	Not lateralized
5/6	2.2 x	1.3:	2.9	(2)//		32	Lt.sided signs predominant?
5/9	2.0 x	1.0:	2.0	(0)		35	
5/13	52 cc. 20% alcohol without effect.						
5/27	2.2 x	1.0:	2.2	(2)		53	
5/30	47 cc. 25% alcohol without effect.						
6/2	75 cc. 25% alcohol.						Drunkenness without sequelae.
6/16	2.2 x	0.8:	1.8	(0)	C	73	
6/25	Excision of cicatrix, right pre-central area.						
7/16	2.3 x	1.6:	3.7	(3)		21	Terminated with light ether.
7/22	2.1 x	1.3:	2.7	(0)		27	
7/25	2.3 x	1.4:	3.2	(3)		30	
7/30	2.2 x	1.3:	3.1	(3)		35	
8/11	2.4 x	1.1:	2.6	(0)		47	

Summary of Post-operative Dosing: A pre-operative dose of 1.8 was reduced to 1.0 at 53 days. Twenty days later a dose of 0.8 failed to produce a convulsion. Alcohol in sufficient quantity to produce drunkenness was without effect, thought it is quite possible that had it been followed shortly by a sub-liminal dose of camphor a seizure might have ensued.

Operative Note: Excision of cicatrix, right precentral region. 6/25/30. J.P.E. A large skin flap was turned down over the decompression site. The subcutaneous tissue was quite adherent to the underlying dura. This in turn was firmly united to the brain so that it was freed about the margins of the wound and the detached portion of dura was left fixed only to the brain. Increased arterial supply

in the region of the wound could not be determined, though the pre-central vein ran into the scar. Anterior to the wound was a small area where the pia-arachnoid had for some unknown reason become firmly fixed to the brain. This small zone was left undisturbed. By faradic stimulation movements of all the extremeties were obtained in a circumscribed region in the immediate vicinity of the scar, in one corroborated instance a prolonged clonic flexion of the contra-lateral fore-arm was obtained, which may or may not have been evidence of a lowered convulsive threshold. Thereupon a block dissection, with sutures, was made of the entire zone responding to faradic stimulation. Difficulty was experienced in cleaning satisfactorily the floor of the excision site, though certainly only a very small amount of scar tissue was left, if any. Dural defect closed with the loose areolar tissue of the scalp.

Summary of Post-excision Dosing: At 35 days 1.3 produced a single convulsion, 1.1 at 47 days had no effect. Therefore at the last observation the minimum convulsant dose lay half way between the pre- and post-operative figures. The result is suggestive, but of course needs confirmation. It is possible that with the passage of time further scarring, and a further reduction in minimum convulsant dose may take place.

Examination of the Scar removed at Operation: The picture is one of a typical wound reaction with musculo-meningeal-cerebral adhesions. The process is still a very active one as witnessed by the large number of phagocytic cells accompanying the ramifying columns of connective tissue which penetrate into white matter. The sections indicate that the scar was not completely removed at the excision.

Summary of the Results Obtained in Monkeys.

1. Camphor in 20% solutions in olive oil given intra-muscularly to monkeys is a reliable convulsant for use over a protracted period of observation. (This finding is in contrast to that for the use of camphor in cats).

2. Simple anchoring of the brain to the skull because of meningeal adhesions failed to lower the minimum convulsant dose of camphor in one animal. The adhesions resulted from opening of the dura followed by immediate closure, an operation undertaken as a control to insure that decompression and opening of the dura has no appreciable effect on the minimum convulsant dose.

3. The infliction of brain wounds in monkeys was followed by a significant drop of the convulsant threshold in five out of eight cases. In two other cases the last camphor dose was given at fifty-three and sixty-six days, and before a decrease in the minimum convulsant dose had developed, and the animals died before being dosed again. In the last of the eight monkeys, a survival animal, there had not occurred a significant drop in dosage at fifty-three days, the last time he was dosed.

4. Operations designed to remove cerebral tissue cleanly were not followed by a drop in the convulsant threshold in four normal animals. Two pre-precentral area excisions, one frontal pole amputation, and one combined frontal and temporal pole tip amputations are included in this group. Rather than a decrease in threshold there was a tendency toward a slight increase. Histological study showed that in the two cases coming to ~~operation~~ post-mortem there was very little post-operative scarring.

5. In two monkeys excision of brain scars was attempted. In one, two attempts resulted in failure. The first attempt was successful in that the scar was completely removed but there followed extensive surgical scarring and the minimum convulsant dose remained low. In the second attempt the scarred tissue was not completely removed and the minimum convulsant dose remained depressed. In the case of the second monkey the minimum convulsant dose followin g scarring was cut in half, after the scar was removed by excision the minimum convulsant dose rose again slightly, This result is suggestive. It is planned to amplify the results of excision of scar tissue in other animals.

6. Note should be made of the fact that in monkeys the post-operative convulsions following camphor dosing almost invariably began with movements of the extremities on the operated, rather than the contralateral side. This was true in both wounds and excisions. It was as if the operation depressed the reactivity to camphor of the cortical cells in the neighbourhood of the operative attack. On the other hand in two animals convulsions were seen to begin on the side opposite the wound a short time ante-mortem, in which instances camphor had nothing to do with the production of the attacks and, of course, faradic stimulation always produced movements of the contra-lateral musculature.

Discussion

A. Experimental Convulsions.

In a preceding chapter the history of experimental convulsions has been reviewed. In the present work no attempt has been made to localize experimentally the centers involved in convulsive seizures. But there has been stressed the increasing evidence accumulating in the literature that seizures may be discharged from various levels, and attention has been called to the importance of this conception in treating cases of post-traumatic epilepsy. Our concern has been with convulsions originating from lesions of the cerebral cortex. Incidental observations among monkeys tend to show that camphor may bring about movements of an athetotic character which resemble closely those seen in humans and which are ascribed to lesions of the basal ganglia. Inasmuch as responsibility for such movements in humans is a much debated subject mention is made of these athetoid gyrations only in passing.

Attention should be called to the fact that among the cats the most exquisite forms of Jacksonian epilepsy were seen. Thus in cats #4192 and #4180, as examples, a definite progression was observed. The first of these animals had a wound of the motor cortex of the left side, the attacks generally began in either the right eye-lid or the right fore-paw, spreading to other muscle groups of the same side and finally involving the muscles of the left side. The second animal's wound was situated in the left occipital region. Time after time attacks were seen beginning with turning of the head to the right with subsequent involvement of right fore-leg and eye-lid

(sometimes one first, then the other), right hind-leg with later involvement of the left side. In many of the cats the Jacksonian type of convulsions developed after a period during which the convulsions had been generalized. This is what should be expected inasmuch as it would take some time for cerebral scarring to progress to the point of producing a focus more sensitive to the convulsant drug than normal tissue. Similarly may the period during which the convulsant dose remains high be accounted for; it is only with the relatively late development of the epileptic focus that the dose drops. That there is a marked variance in the period of time required for the development of focal convulsions is indicated in the results, some of the cats never being observed to have other than a generalized seizure during the entire period of observation. Also it was noted that there might be an alteration in the type of convulsion later ~~both~~ in the animals' histories, attacks of generalized or of focal onset occurring variably.

Among the monkeys a different type of convulsion was seen. Whereas the pre-operative attacks had been always bilateral, with one exception as had the cats's seizures, the post-operative convulsions different from those seen in the cats. In almost all of the cases the post-operative convulsions began focally within a very short time. Almost invariably they began on the same side as the wound, instead of the contra-lateral side as would be expected. Contra-lateral movements were, of course, obtained on direct faradic stimulation of the cortical motor centers. We are unable to offer a satisfactory explanation of this fact.

The lowering of the convulsant threshold following brain wounds in experimental animals has, of course, been known for nearly a century. The conception that the clean removal of cerebral tissue in animals raises the threshold is a much more recent one, and was first clearly indicated by Muncie and Schneider (1928), though in the preceding year Sparks had made a similar observation. There was sought in the present study a histological explanation for this difference in reaction. For if the clean removal of cerebral tissue in an experimental animal raises the convulsant threshold whereas a scar lowers it, the excision method as applied to cases of post-traumatic epilepsy might be placed on a more rational, and experimentally supported basis. Moreover, by such a study it might be possible to discover technical details of importance in handling such cases.

B. Principles of Technique.

(1) Vascular Supply: Confirmation of Muncie and Schneider's findings has been made though the increase in convulsant threshold has not been so striking in the excisions included here as among those reported by the earlier authors. Furthermore, it has here been shown that operative attempts at clean excision have not always met with success but that sometimes rather severe scarring has followed an excision. The obvious explanation would be that sufficient trauma has been done at the operation, or that enough devitalized tissue was left behind to account for the different reaction. However, the operative notes do not confirm this assumption and in at least one excision whose threshold was raised post-operatively, there comment was made on the fact that all the devitalized cerebral tissue could not be removed at operation (Cat #4105).

From a comparison of two excisions with contrasting histological pictures and convulsant results (Cats #4135 and #4159) may be drawn an important conclusion. The first was a shallow excision. The site has filled in with a loose proliferation of connective tissue and the entire block of grey matter bounded on either side by lines drawn down at right angles from the surface at the margins of the excised area and reaching to the white matter, is filled with degenerated tissue infiltrated with small capillaries and phagocytic cells. On the other hand the second excision removed a block of cerebral tissue extending down into the white matter. Interference with the vascular supply seemed the most likely explanation of the difference in operative results. Penfield in a personal communication has suggested that unless the depth of the excision be such as to include all the tissue supplied by the small capillaries running into the brain at right angles from the pia, that is, unless all the grey matter down to the fiber tracts be removed, there is bound to be left tissue deprived in large part of its blood supply. Such would seem a logical explanation of the difference in a histological picture outlined in these two instances. Corroboration of these results has been found in monkeys.

There must be stressed then the necessity of an adequate depth of excision which means inclusion of all the grey matter down to the fiber tracts, the size of the block at this depth being very nearly if not exactly the same as that at the surface. In those instances in which partial or complete amputation of a pole is done there is obviously no severe interference with vascularity so long as the

transaction is carried at right angles to the surface. It is conceivable that were the cut carried at a more acute angle there might be left residual tissue deprived of its proper blood supply. Such tissue would become invaded by capillary ingrowth, and phagocytosis of the degenerated tissue would occur, to be followed at a later stage by scar tissue contraction.

(2) Operative Handling of the Meninges. In most of the brain wounds of the present series the dura was left unclosed at the wound site, in some instances was excised. In the excisions, on the contrary, an effort always was made to close the dura. This was done because it was felt that the absence of dura would tend to promote adhesions, and that its presence might serve in a measure to prevent them. As a matter of fact, in the single control monkey in which anchoring of the brain to the skull was produced through musculo-meningeal-cerebral adhesion (#4240) the adhesions exerted no depressant effect on the convulsant threshold. While it is totally unjustifiable to draw conclusions from a single case it is our impression that "anchoring" of the brain, as spoken of by Sargent, plays no part of itself in the lowering of the convulsant threshold in animals.

In experimental brain wounds with cranial defects the adherence of the meninges and brain to the extra-cranial tissues is of such a degree as to make the inclusion or exclusion of the dura of trifling importance. Likewise among the excisions with cranial defects the union of the extra-cranial tissue with the firmly united dural flap and proliferated arachnoid, is such as to suggest that the preservation of the dura is of little importance from a histologic standpoint.

It has been pointed out in the chapter on Wound Histology that if the pia-arachnoid is damaged adhesion follows between the pachy- and lepto-meninges. Injury to the pia-arachnoid is an unavoidable concomitant of excision and meningeal adhesion is an invariable histologic sequence. Our experimental experience is too limited to judge of the importance of the dura when a bone flap is replaced but, in general, it is our opinion that the only indication for the preservation of the dura in any case is that it may act as an additional barrier to infection.

The degree of arachnoidal proliferation seems to vary directly with the demand for phagocytosis. In those instances in which little damage has been done at operation the reaction is slight. On the other hand an extreme of connective tissue reaction may be seen as in #4240, an eleven day wound in which there is great vascular ingrowth. (Photography) True, a good deal of the connective tissue of such an early wound stage would disappear later without leaving a trace, yet the ultimate scarring in this monkey's brain, had it lived, would undoubtedly have been severe.

If the demand for arachnoidal proliferation has not been great, the pia or its corresponding connective tissue structure lines the cyst with a single layer of cells. If the vascularity is marked, however, pial relations become extremely difficult to follow.

(3) The Value of Excision of Cerebral Scars in Experimental Animals.

As to the efficacy of scar excision in experimentally induced traumatic epilepsy little has so far been said. There can be no doubt that brain scars reduce the convulsant threshold, nor can there be doubt that surgically correct removal of cerebral tissue does not result in a lowering of the threshold. But that excision of a brain scar in an animal which has been subjected to repeated convulsions will raise the convulsant threshold back to normal, is a question which it is not possible to answer from the data at hand. Excision of a scar in one monkey in the present series failed to achieve that objective because of the occurrence of further scarring induced for an uncertain reason by the excision procedure. In a second monkey a suggestive but indefinite result was obtained. Further experiments are being carried on to determine this question.

It is conceivable that the excision procedure will fail to achieve the desired result for it may be that with oft-repeated convulsions the animal may acquire the "epileptic habit", a term which is subjected to much abuse. It is a means of avoiding for another period consideration of the physico-chemical reactions, or morbid physiology, which must underlie the epileptic seizure, a physiologic state which may well be beyond the power of a local procedure such as a scar excision to relieve.

More and more evidence is accumulating to point to the cerebral vasomotor system as the agent through which the altered cellular reactions responsible for the epileptic discharge are brought about. Eventual control of the vascular reactions of the cerebrum suggests itself as a more hopeful means of attack than excision of scarred areas, although excision procedures may still have a place in those cases where progressive brain damage must be prevented.

In conclusion it is only fair to draw attention to the fact that the analogy between experimentally produced convulsions and those of genuine traumatic epilepsy must not be drawn too closely. The action of camphor is probably a direct one on the cortical cells, that of wormwood is probably the same. The mechanism of true traumatic epilepsy is unknown. Yet bearing in mind the reservation that induction of seizures by the use of convulsant drugs in animals with artificially induced brain changes is probably a poor makeshift attempt to duplicate true traumatic epilepsy, much may be expected of the experimental approach to the problem.

Summary.

1. An experimental approach to the problem of traumatic epilepsy is outlined.
2. The early history of traumatic epilepsy is reviewed.
3. The literature on experimentally induced convulsions is summarized and the levels of epileptic discharges are discussed.
4. The literature of post-traumatic epilepsy, both of peace and of war times, is reviewed.
5. The histologic aspects of brain wounds and of the clean excision of cerebral tissue are summarized.
6. The results of an experimental study are given. In one series of animals, cats and monkeys, the effect of brain scarring on the threshold of convulsant drugs was determined and the resultant histology was studied. In a similar series there was contrasted the effect of the surgically clean removal of cerebral tissue upon the convulsant threshold. The resultant histology is compared with that of the previous group.
7. The conclusion is drawn that brain scarring lowers the convulsant threshold of experimental animals. The converse that when brain scarring is absent or minimal the convulsant threshold is not lowered is also concluded.
8. That the removal of a cerebral scar returns the lowered convulsant threshold of experimental animals to normal has not as yet been determined.
9. Surgical principles involved in the excision of cerebral scars are discussed.

My thanks are due to Professor Wilder G. Penfield for his thoughtful help and criticism and for the extension of every facility for the completion of this work, likewise to Assistant Professor William V. Cone for ever helpful advice and assistance.

Appreciation is expressed for the courtesy of Professor Jonathan C. Meakins and Assistant Professor C.N. H. Long of the Department of Medicine who gave generously of their laboratory space, making possible the proper care and maintenance of a large number of animals.

This research has been done under tenure of a Madeleine Ottmann Fellowship for Research in Epilepsy.

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