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THE UNIVERSITY OF ALBERTA

THE EFFECT OF SUBPIAL VERTICAL CORTICAL INCISIONS ON A COBALT-GELATIN FOCUS

by

© JACQUES E.J. DUYSENS

A THESIS

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled The Effect of Subpial Vertical Cortical Incisions on a Cobalt-Gelatin Focus submitted by Jacques E.J. Duysens in partial fulfilment of the requirements for the degree of Master of Science.

D. L. McRae M.D.
.....
Supervisor

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Date.....

ABSTRACT

The effect of subpial cortical isolation (without undercutting) on an epileptic focus was examined.

In total 37 cats were used in these experiments. A small amount of cobalt-gelatin material was used to create a focus over the motor cortex. Later, a second operation was performed in which four subpial cuts were made, 2 mm deep, forming a square 2 x 2 mm around the focus.

No spikes could be seen over the focus post-operatively, while in another series, in which sham operations were done, spikes persisted at least one day following surgery. It was concluded that subpial isolation was very effective in preventing spike generation. This finding was explained by assuming that the cortical incisions reduced the neuronal mass available for hypersynchronization. Furthermore, it was found that these subpial transections did not result in a change in paw preference, indicating that no detectable functional damage was caused by this surgical technique.

It thus seems that the described method is superior to topectomy, both functionally and electroencephalographically.

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I. INTRODUCTION

The classical surgical techniques for the treatment of focal epileptic lesions have severe disadvantages. Removal of the abnormal brain tissue, topectomy, results in a functional deficit depending on the size and the location of the removed area. A solution to this problem was offered by Morrell and Hanbery (101) who described a new technique using subpial vertical cortical incisions. The cuts, which were 3-5 mm apart, formed a grid over the epileptic area. Since no cortical tissue has to be excised, and since good functional and clinical results were obtained on three patients, it seems worthwhile to further develop this approach.

One way of doing this is to go back to animal research in order to find an experimental verification of the observations of Morrell. What is the effect of subpial transections on the hypersynchronization activity of a focus? Both Burns (18) and Petsche and Rappelsberger (108) suggest that the tendency to synchronization is a function of the size of the concerned area. Thus one can assume that epileptic spikes require a critical cortical volume and that cross-hatching of the focus decreases the number of neurons available for hypersynchronization. Such an explanation throws some light on the observation of Tharp (137) who found, in rabbits, that a focus which was completely isolated by four subpial cuts to the ventricle was characterized by a "refractoriness to the development of epileptiform activity after the initial reapplication of the penicillin pledget".

Our working hypothesis, based on the belief that a critical volume of neurons is necessary to the generation of hypersynchronous activity, requires several additional assumptions.

- First, it is supposed that spike generation is a characteristic feature of the epileptic focus and that its mechanism lies entirely within the cortex. Consequently, any action against spike generation will considerably alter the behaviour of the focus.

- Secondly, if non-synaptic spread and volume conduction are the main ways of communication in a focus, subpial transections are inefficient.

- Thirdly, it is assumed that vertical cortical subpial incisions do not cause significant functional damage.

These three assumptions will be examined in the next three chapters.

II. THE CORTEX AS A SOURCE OF EPILEPTIC ACTIVITY

In this chapter the problem of the origin of epileptic activity as seen in an EEG focus, will be discussed.

Is the paroxysmal activity due to cortical or subcortical mechanisms?

And, if the cortex is responsible, what part of the cortex: isolated epileptic cells or epileptic aggregates?

A. Cortical Synchronization and Rhythmicity

A distinction has to be made from the beginning between the concepts of "synchronization" and "rhythmicity". Synchronization in this thesis refers to the simultaneous firing of a large number of cortical neurons, resulting in an EEG spike. Rhythmicity is a term for the recurrent appearance of certain EEG characteristics. In experimental foci there is usually synchronization (single spikes) first and later rhythmicity (after-discharges).

The question to be answered is: What is the role of the cortex and the thalamus in both synchronization and rhythmicity? We will first consider the cortex and later direct our attention to the thalamus.

i. The cortex

It seems beyond any doubt that both spikes and after-discharges arise in the gray matter of the cortex (13). For example,

cortically applied KCl (causing spreading depression) abolishes both (55). This is easily understandable, since intracellular experiments have shown that spikes and after-discharges arise from the same neuronal elements (31, 59, 94, 126). However, Feher et al. (40) claim that the site of origin of spikes and after-discharges could be quite different. They conclude that synchronous discharges, evoked by strychnine or d-tubocurarine, have their origin in the upper 300-600 μ thick layer of the cortex, while rhythmic after-discharges originate in layers IV-V of the cortex. In their opinion, these after-discharges are due to reverberation of impulses in closed circuits which are strictly intracortical.

Further support for the idea that both synchronization and rhythmicity have their origin in the cortex is found in studies on isolated cortex. Indeed, the self sufficient role of the cortex in the generation of synchronous electrical activity is best illustrated by the fact that undercut cortex is still able to exhibit EEG and single unit activity (12, 46, 70, 75, 80, 139). In isolated cortical slabs, Morrell and Torres (102) found that electrically induced after-discharges could be observed, which did not spread deeper than the dendritic layer. In another study (47) in which the EEG-intracellular relationship was investigated, it was clearly proven that isolated cortical slabs still show neuronal synchronization. Even complex patterns, such as 3 cps spike and wave discharges, can be seen in isolated cortex, having no connections with subcortical structures (34, 68). Furthermore, experiments using explanted CNS tissue cultures also demonstrate the amazing synchronization properties of the cerebral cortex. Reaggregates of cortical cells can generate after-discharge patterns, evoked as well as

spontaneous (26).

Thus, it seems clear that: (i) the potential for generating both spikes and after-discharges lies in the cortex; (ii) neuronal synchronization and rhythmicity is possible in the cortex without any intervention from the thalamus or other subcortical structures.

But this does not imply that in reality the thalamus is not involved in this mechanism. As will be seen now, the thalamus is, in fact, very important in cortical rhythms.

ii. The thalamus

Today it is widely accepted that the thalamus is involved in producing alpha waves (2). But the role of the thalamus is less clear in other rhythmical events such as after-discharges. Nonetheless, most authors (71, 79, 147) believe that the thalamus plays a substantial role in cortical epileptogenesis.

In order to give a more explicit formulation of the problem, we will split the issue into two parts: the influence of the cortex on the thalamus and vice versa.

a. Cortex to thalamus

Cortical discharges can spread to the thalamus in two ways: orthodromically via axon collaterals, or antidromically via thalamocortical efferents (20, 62, 124). Gutnick and Prince (62) recorded bursts of spikes in thalamocortical relay neurons whose axons project into a penicillin induced cortical epileptigenic focus of a cat. The bursts of spikes were coincident with the spontaneous surface epilepti-

form discharges.

It is further known that in the absence of a pathway for intracortical spread of the epileptiform discharge, the activity remains highly restricted to the functionally related thalamic nucleus (61).

Today, no answer can yet be given to the question of exactly what constitutes the mechanism of cortical impulse generation (ephaptic depolarization? increase in extracellular potassium?). But more and more investigators assume that such impulses can antidromically influence thalamic neurons (56, 62, 124).

b. Thalamus to cortex

The specific thalamocortical projections especially are important in modulating the output of epileptic pyramidal neurons (119). Purpura (120) reaches the conclusion that even while there may be pacemaker like processes involved in focal epileptogenic lesions, such foci must be influenced by multiple synaptic inputs from the thalamus. But what exactly is this "modulating" and "influencing"?

Recently (55) it was suggested that the thalamus acts specifically on the rhythmicity of epileptic events. This is convincingly illustrated by the following observations:

1. KCl depression of the thalamus abolishes the cortical after-discharges but has no fundamental effect on the initial hypersynchronization (spikes) caused by application of penicillin, cobalt and Metrazol (3, 55).

2. Grimm et al. (55) divided the motor cortex of monkeys with a wedge of film up to a depth of 6 mm. On one site of the barrier they placed penicillin while the other site served as the "control". A penicillin spike at the focus produced an evoked potential at the control site with a latency of 5-6 msec, followed by an after-discharge burst.

3. When this experiment was repeated while spreading depression was initiated in the ipsilateral thalamus, the authors observed that the focus continued to discharge but that no evoked potential or after-discharge was seen at the control site.

4. Application of KCl (causing spreading depression) at the penicillin focus resulted in the disappearance of the after-discharge both at the focus and at the control site. The short latency of this effect at the control site is not accounted for by the SD wave passing around the sectioned cortex.

From these studies it becomes evident that the thalamus has a different action on the paroxysmal discharges (spikes) than on the after-discharges. Depression of the thalamus results in a complete disappearance of the after-discharge and in a reduced spike firing rate at the penicillin focus. Thus, the thalamus in some way has a role in the rhythmic behaviour of the cortex.

The general idea which arises from the experiments of Grimm et al. (55) is that paroxysmal cortical events can reach thalamic

neurons, where a rhythmic discharge is generated, and send back to the cortex as a cortical after-discharge.

However, much more investigation is required to confirm this hypothesis. For instance, in Grimm's model, it is assumed that the rhythmicity of the cortical after-discharge has a thalamic origin. But there is evidence that the cortex is able to produce rhythmical activity on its own, providing that a trigger stimulus is present (vide supra). Therefore it seems reasonable to assume that the thalamus acts as a relay station for the stimulus which is required to trigger the inherent rhythmicity of the cortex. It is not possible to refute this alternate hypothesis on the basis of Grimm's experiments.

Whatever the right mechanism, several points can be made thus far:

I. At the cortical focus the appearance of after-discharges is preceded by a period of synchronous hyperactivity (spikes).

2. It is most likely that these original paroxysmal events have a strong influence on thalamus structures, which are then able to trigger after-discharges in the focus.

3. To break this circuit it would be sufficient to prevent the early hypersynchronization in some way.

Before testing this latest hypothesis, it is necessary to have more information about the basic elements involved in hypersynchronization.

What is the fundamental entity in a spike generating focus? This question will bring us to a description of the "epileptic aggregate".

B. The Epileptic Aggregate

If the cortex is so important for synchronization, what constitutes the basic cortical entity in epileptic hypersynchronization?

It is evident that epileptic activity implies the firing of many neurons. Even a simple strychnine spike requires the cooperation of both middle and deep layered neurons (37). But is this epileptic activity due to the abnormal behaviour of single epileptic neurons with subsequent recruitment, or is it due to a group of epileptic neurons?

Today, more and more investigators think that the units of synchronization correspond with vertical columns, formed by closely interconnected cortical neurons. Jasper (71) suggested that these vertical columns may be the same as the functional columns found by a number of neurophysiologists (66, 67, 103, 114). He found some support in the work done by Binsky (113), who described a dipole with about the same dimensions as the cortical columns of Hubel and Wiesel, as being the minimal entity to maintain an epileptic discharge. Petsche and Rappelsberger (108), who studied potential fields in the cortex of rabbits, concluded that the morphological elements of synchronization called "vertical dipoles" may have a diameter of less than 1 mm. The dipole concept is largely based on the well known observation that there is a phase reversal in the EEG activity when recorded simultaneously with epi- and subcortical electrodes (85). For instance, a

depolarization of the soma region is correlated with a hyperpolarization of the apical dendrite arborizations. Raabe and Lux (122) and Elul (36) assume that one or two interneurons are responsible for this correlation.

Recently (111), it was suggested that the superficial layers act as a low-pass filter. This could imply that the functional cortical generators end a few hundred micra below the surface. Further evidence for the existence of vertical dipoles in epilepsy is given by Gumnit et al. (60). In the center of the focus they found surface negativity but the maximum negativity was found in layer 5 of the cortex. In the periphery there was a surface positivity in combination with a deeper negativity, which was also located in layer 5. In relation to the question of ephaptic (non-synaptic) transmission, the authors felt that ephaptic influences, if any, were probably linked to the cells forming the vertical dipoles, because they observed some independence of nearby dipoles.

In conclusion, the basic cortical generator of epileptic activity is formed by a vertical column of densely packed neurons. The hypersynchronization as seen in EEG recordings at an epileptic focus is the result of a synchronous discharge of a group of such columns or dipoles.

Theoretically, it should be possible to distort or prevent such spike generation by interfering with the connections between the different dipoles. An obvious way to do so is by making vertical incisions into the cortex.

III. THE INTRACORTICAL SPREAD OF EPILEPSY

In the previous chapter it was seen that cortical neurons are able to fire in a synchronous manner. The next step will bring us to a consideration of the mechanisms underlying synchronization. As stated by Petsche et al. (111), brain potentials are the result of two basic conditions: volume conduction (i.e. "conduction in an electrically inactive electrolytic conductor") and active conduction ("comparable to the one of action potentials in nerves"). When an EEG is recorded from a human scalp there is no doubt that the skull and the brain act as a volume conductor. However, the problem is different when we study the electrical activity at its origin. A spike, as seen on the EEG, is the result of the synchronous firing of a large set of neurons. The coherence can be due to the fact that one neuron excites another neuron via synapses but it is also possible that neighbouring neurons are activated by the electrical field produced by the original epileptic elements. This issue: synaptic or ephaptic (non-synaptic), is highly controversial and simple answers cannot be given. Moreover, it is well possible that the relative role of volume conduction and synaptic propagation is different when studied in a plane perpendicular or parallel to the cortical surface.

In the opinion of Petsche et al. (111) passive conductivity is more important in the horizontal than in the vertical (surface to depth) direction. Apparently, the best method to examine this issue is the transection of the cortex, since it is expected that an incision in a volume conductor has little effect on synchronization

but causes serious disturbance in synaptic propagation.

When tracing the idea of non-synaptic conduction, it seems necessary to make a distinction between ephaptic mechanisms at specialized electrotonic junctions (8) and ephaptic effects produced by current flows in extracellular spaces and across contiguous neural membranes (120). The former phenomenon is best illustrated in the earthworm (73), crayfish (48, 83, 152), Mormyrid electric fish (8, 9) and chick (93), while the latter has been found in the mammalian CNS. Nelson (104) showed that the excitability of motor neurons can be changed by the field effects of adjacent motor neurons which were antidromically activated.

The tight junctions were called "macula occludens" (39) or "nexus" (30). They are also common in epithelial and glial tissues (39), where electrical spread can indeed be observed (82, 90). This brought Grundfest (56, 57, 58) to the idea that ephaptic transmission in the cortex could be "an evolutionary remnant, recalling the epithelial origin of the nervous system".

Non-synaptic transmission is mostly found in situations requiring synchronization of many neurons. Epilepsy is undoubtedly an example of such a situation and Grundfest (56) pointed out that it is conceivable that some pathological conditions may lead to membrane fusion between cortical neurons, thus resulting in a tendency to hypersynchronization.

Two articles are commonly cited in general reviews (71, 79, 148) in support of the ephaptic hypothesis:

- Libet and Gerard (86) demonstrated that caffeine induced waves could

cross a cut in the isolated frog brain. However, a slight separation of the cut halves, connected only by Ringer solution, did block the wave. The authors supposed that the opposite results, obtained with strychnine waves (32) and also with epileptic spread (38) were due to species differences or to the poor apposition of the cut surfaces. However, in a later publication, Libet and Gerard (87) admitted that the spread across the cut could simply be due to the fact that the whole brain was soaked with caffeine, thus increasing the excitability of cells on both sides of the cut.

- Bremer (11) showed that synchronization of strychnine spikes remains in the upper and lower parts of a completely transected spinal cord.

Some investigators have felt that their results could best be explained by ephaptic spread of epileptic activity (37, 54), the most likely site of transmission being the dendrites. Mountcastle stated: "The large and interlocking dendritic fields of cortical cells provide an optimal geometric arrangement for ephaptic effects". But electron microscopic studies (155) have revealed that the dendrites of normal cortex are probably totally invested by synapses, thus implying that the dendrites are electrically inexcitable.

Ward (149) proposed two solutions. First, he stressed the importance of non-dendritic tissue, e.g. glial, in the epileptic spread, and secondly, he suggested that the dendrites of epileptic neurons have relatively less synapses and are more electrically excitable. This latter effect could be the result of a partial deafferentation of the epileptic cortex. Jasper (71) sees the function of

epileptic potential fields in a facilitation and synchronization of discharges in large areas of the cortex, although he admits that, in general, synaptic mechanisms play a leading role which could be especially true for the synchronization of seizure activity in the hippocampus (120). In this region large field potentials (10-20 mV) are seen in association with intracellular spikes, and it is thought that synaptic induced discharges in the dendrites may ephaptically influence neighbouring neurons.

On the other hand, Purpura et al. (118) presented strong evidence against the ephaptic spread of epileptic activity. Upon splitting an epileptic lesion, he found that synchronous activity was no longer obtained from both halves. Application of various pharmacological agents on one side of the cut did not affect the activity of the other side.

These observations are in conflict with results obtained by Torres (138, 139). This author reported that propagation of epileptiform activity across a neural discontinuity into isolated cortex is possible. If this isolated slab is previously sensitized by an epileptogenic agent, electrical after-discharges initiated in the surrounding cortex generate an independent after-discharge in the slab.

When similar stimulation (strychnine and electrical current) was applied to the isolated slab, the epileptic activity remained localized in the isolated slab. Torres (139) explains his results by the principle of volume conduction. To understand the fact that the propagation occurred only from the outside to the inside, both Torres (139) and Morrell (99) stress the difference in neuronal mass

between the two areas. Only when a large mass of neurons is stimulated the after-discharge is strong enough to cross the neuronal interruption into the relatively small number of neurons within the isolation. In his own experiments, Morrell (100) used tetanization as the stimulus. Again, non-synaptic transmission is invoked to explain the inward spread of the tetanization effect.

Thus far it can be said that the experimental evidence for ephaptic conduction of epileptic activity is only convincing in some exceptional cases where epileptic activity has to go from a larger neuronal volume to a smaller one. Thus, the ephaptic hypothesis is largely supported in speculative models of epilepsy, but experimental data are lacking.

On the contrary, the results of some investigations strongly suggest that ephaptic spread or volume conduction has almost no role in the propagation of epileptic activity.

A first set of data comes from the study of penicillin induced focal spikes. Goldensohn et al. (52) investigated the potential field of a penicillin focus by means of a rectangular array of 12 electrodes with 2 mm intra-electrode spacing. They found that the behaviour of the penicillin electrode was quite different from all others. For instance, while increasing negativity was recorded at the focus, the surrounding electrodes showed a predominantly positive spike. Such an observation, also mentioned by Tharp (137) and by Gumnit and Takahashi (58), is difficult to explain in terms of electronic field potentials.

Identical conclusions were reached by Tharp (137), who also used electrodes 2 mm apart. An acute epileptic focus was created by

application of penicillin to the sensory motor cortex of 21 adult rabbits. In most animals a very steep voltage gradient was observed and the spike was confined to within 2 to 4 mm of the focus. The gradient was steeper anteriorly, indicating that the tangential spread is preferentially to the posterior head region. Latency measurements were done, using several techniques, and the author felt that the variability of the results could best be explained on the basis of synaptic transmission, rather than volume conduction. More support for this conclusion was found in the observation that procaine altered the behaviour of the focus, but did not alter the ability of the focus to influence neighbouring cells. The appearance of surround spikes without centre spikes is hard to understand on the basis of volume conduction.

However, Tharp admitted that volume conduction contributes to a certain extent to the spread of epileptic activity. Indeed, a low voltage spike was recorded 2 mm posterior to a focus which was isolated by vertical subpial transection. Such transection failed to interrupt the spike spread when made at a depth of 0.8 or 1.7 mm. Only complete isolation with cuts to the ventricle was efficient in blocking the transmission. This lead the author to the conclusion that deep cortical association fibers are responsible for the propagation of epileptic activity.

In other cases, however, it has been shown that trans-cortical spread is of primary importance. Petsche and Sterc (112) showed, also in rabbits, that some seizure waves could spread throughout undercut cortex without any help from deep association

bundles. Moreover, Morrell (101) reported a new surgical treatment for focal epilepsy using purely cortical incisions. He made vertical subpial cuts 3 to 5 mm apart in the cortex of three patients with focal epileptic lesions, and found that no clinical or encephalographic epileptic signs were seen following surgery. Again, this could indicate the dominant role of the transcortical connections in the spread of epileptic activity.

Results similar to those of Morrell were obtained in monkeys by Erickson (38), who demonstrated that the spread of the epileptic discharge can be limited by transcortical section. For example, the epileptic propagation along the motor strip can be partially interrupted by a cortical cut between the arm and leg area. Van Harreveld and Stamm (142) confirmed the findings of Erickson. They stated that it is possible to reduce or even abolish an after-discharge by cutting the cortex between stimulating and leading-off electrodes. Later, Ferrari and Galasso (41) found that cocainizing a narrow circle around a strychnine focus in dogs does not modify the focal activity, but prevents the fit from spreading.

Very interesting work was also done by Petsche and Rappelsberger (108), who used transverse and longitudinal vertical incisions in the cortex of rabbits. These cuts rendered seizure patterns heterogeneous in both wave shape and frequency on the two sides of the cut. However, it has to be mentioned that the parameter of the depth of the incision was not studied systematically and that, as noticed by Torres (139), some of the figures of Petsche and Rappelsberger (108) show the presence of low amplitude spikes in the

electrodes which are closest to the incisions, indicating that volume conduction could have contributed.

The deeper layers are especially important in the spread of epileptic activity, as incisions have to be made fairly deep in order to disturb the spread of epileptic activity. This is in agreement with the idea of Adrian that self-sustained after-discharges occur at the layer of the basal pyramidal dendrites. Also, Burns (18) indicated that burst responses in isolated cortical slabs cannot be interrupted if cuts were only made through layers 1 to 4.

In summary, it seems that the role of ephaptic transmission and volume conduction is rather limited in epileptic phenomena. Only in two cases can we assume that ephaptic conduction in the cortex is important:

1. When epileptic activity is driven from the surrounding cortex into an isolated slab.
2. At the centre of the focus, at the site of the spike generation and in the immediate neighbourhood, it is possible that ephaptic transmission accounts for the sudden hypersynchronization.

But it is obvious that the first case is highly artificial and that in the second case only a rather limited neuronal mass is influenced by ephaptic or volume conduction. The main method by which propagation of epileptic activity occurs is synaptically, as is proven in many experiments in which transcortical incisions could significantly alter the epileptic spread.

IV. THE INFLUENCE OF VERTICAL CORTICAL SUBPIAL INCISIONS ON THE FUNCTION OF NORMAL CORTEX

This chapter is concerned with the possible functional damage caused by subpial cuts in the cortex.

Is it possible to make such transections without disturbing the complex organization of the neocortex? The extensive investigations of Sperry allow us to give a positive answer to this question.

In a first experiment, Sperry (130) made multiple vertical cuts in criss-cross patterns on the sensory, motor, and neighbouring cortex of monkeys. When the white matter was not damaged, such lesions failed to give important deficits. And even with a minor involvement of the white matter there was no impairment of motor function after 3 1/2 weeks after the operation. Sperry explained his results by claiming that his slicing produced only minor damage to the cell bodies, and left intact the majority of association fibers and the primarily vertical connections of the neurons. Meanwhile, the functional organization in radial columns of neurons has become a well known characteristic of the motor sensory cortex.

Later, Sperry (133, 134) repeated his experiments, this time in the visual cortex of cats. Subpial slicing as well as the implantation of metallic wires did not result in a marked disturbance of visual pattern reception. These results are concordant with those of Lashley et al. (84), who found that visual perception in the monkey remains after short-circuiting the striate cortex with overlaid gold

bands and other conductors.

On the other hand, when a dielectric material (such as small plates of mica) was implanted in the same area of the cat's cortex, some perceptual disturbances were noticed. But Sperry (134) noticed that this is due to destruction of the white matter and not to distortion of electric fields. Indeed, control knife-cut lesions, simulating the tissue damage by mica inserts, did not produce smaller functional deficits.

Thus, the question arises: Why can the cortex function so well without transcortical connections? The answer to this question comes mainly from our present knowledge about the functional organization of the cortex in vertical columns (66, 67, 103, 114). Morphologists have tried to find structural analogies to these columns. So far, the most promising evidence comes from recent work done by Fleischhauer et al. (44). Their investigations with electron microscopy revealed the existence of vertical bundles of dendrites in the sensory motor cortex of both rabbits and cats. Moreover, the dimensions of the functional columns are in good agreement with those of the vertical bundles of the apical dendrites.

The general idea which arises from all of these studies is that the cortex constitutes a grid of densely packed vertical columns with a high degree of mutual interconnections. Functionally, it seems that the cortex can operate quite well when some of these transcortical interconnections are interrupted.

V. MATERIALS AND PROCEDURE

A. The Experimental Model

Several chemical agents were tried in this experiment to create the best possible focus. Two requirements had to be fulfilled to give a good experimental model of chronic epileptic lesions:

(a) the focus had to exist for a certain period of time;

(b) the concomitant brain damage had to be limited because the same area had to be used subsequently for surgery.

Alumina cream and cobalt powder failed to satisfy both requirements, but the use of cobalt-gelatin discs was successful.

1. Aluminum Hydroxide

Aluminum cream proved to be an excellent epileptogenic agent in monkeys. In cats, however, the results are more ambivalent, and an extensive study on this topic was only recently published by Velasco et al. (143, 144).

Two methods were used in our experiments:

(a) Three cats received a single injection of 0.03 cc Aluminum hydroxide (Fisher, A-583) in the motor cortex. A stereotaxic device was used to bring the chemical 3 to 4 mm below the pia.

(b) A commercially available alumina cream preparation (Amphojel) was sterilized and injected into the motor cortex in different amounts. One cat received 0.1 cc, a second 0.25 cc and a third 0.6 cc.

ii. Cobalt powder

The use of aluminum hydroxide has several disadvantages:

(a) the long latent period (from 15 to 45 days);

(b) the unpredictable development of the focus when small amounts are used in cats.

On the other hand, cobalt foci are characterized by a short latency and a relatively short time course (64).

Four cats were given Diabutal anaesthesia and then operated upon. The dura was opened and the sterilized cobalt powder (Fisher C-263) was placed on top of the motor cortex. One animal received 75 mg, another 50 mg and two had 25 mg. The dura was sutured and recording screws were placed, as will be described later.

iii. Cobalt gelatin discs

Several investigators have tried to modify the cobalt method in order to avoid the severe necrosis resulting from intracerebral application and to slow down the time course of the focus. Payan et al.

(106) used five groups of rats. One group received no treatment, the others received metallic cobalt powder on top of the dura (extradural), on the surface of the brain (subdural), implanted in the brain (intracerebral), or applied over the remaining layer of skull, which was partly drilled (extracranial). Extracranial cobalt proved to be less effective but both extracranial and extradural cobalt caused less necrosis and fewer abscesses.

Fisher et al. (42) found another method to delay the onset of the epileptogenesis by implanting pellets of cobalt-gelatin suspension intracortically. A combination of the techniques of Payan et al. (106) and of Fisher et al. (42) was used in the experiments of Malzone et al. (91) on cats. These authors mention four groups: (1) no lesion, (2) subdural disc, (3) epidural disc, and (4) extradural disc, which corresponds with Payan's "extracranial" group. The investigations of Malzone et al. (91) were taken as the basis of the research which is reported here. Exactly the same preparation of cobalt-gelatin discs was used and a similar division of groups was made:

(a) The extradural group consisted of four adult cats. The skull bone over the motor region was drilled part way through without perforating the tabula interna. A 10 mg cobalt-gelatin disc was then placed in the hole which was further filled with bone wax.

(b) The epidural group was formed by 16 cats, divided into two subgroups (Table 1). Six cats underwent a sham operation at different intervals following epi-

dural implantation. Nine cats had subpial transsections around the previously created focus. It should be noted that one cat was first operated with subpial transsections and four days later cobalt-gelatin was placed in the center of the isolated slab.

(c) The intracortical group (four cats) is split into two parts: Two control cats had only one surgical intervention (the subdural or intracortical application of cobalt-gelatin); two cats underwent subpial isolation of the focus one day after cobalt implantation.

B. Surgical Technique, Recording, Stimulation and Histology

1. Surgery

All cats were anaesthetized with intravenous injection of 25 mg/kg diabutal (sodium pentobarbital). After the head was shaved hair removing cream (surgex) and later antiseptic material were applied to the skin. A midline incision was made over the skull and bleeding was controlled by coagulation.

With the aid of a dental drill large openings were made in both frontal sinuses. These were subsequently packed with gelfoam. The skull over the frontal sensory motor cortex was now visible and a small hole could be burred over the forepaw area. On the side opposite the preferred paw (paw preference testing: see later) cobalt-gelatin was implanted in the 0.5 x 0.5 mm hole. Bone wax was used to stop bleeding.

The location of the forepaw region was determined using information from stimulation and ablation experiments on the sensorimotor cortex of cats (45, 88, 156). A special electrode, consisting of phonograph wire with a soldered tip, was inserted in the same hole on top of the cobalt. A similar electrode was placed in the hole over the homotopical region. The electrodes were held in place with Kerr Formatray acrylic and the same material was used to close the sinuses after removal of the gelfoam.

Four 4 mm stainless steel skull plate screws (Howmedica nr. 6484-0) were then placed symmetrically over the parietal and occipital areas. An additional screw was placed over the frontal sinus as a ground. The phonograph wire, which was attached to each screw, was soldered to an Amphenol seven channel recording headplug. Both screws and headplug were enveloped in an acrylic mold. The scalp was sutured and 1 cc Derapen (one shot penicillin) was given I.M.

The EcoG was recorded at several intervals during the 24 hours following surgery. Having clinical or electroencephalographic proof of an epileptic focus, a second operation was started.

After injection of the anaesthetic, the scalp was opened again and the acrylic removed from the sinus on the side of the focus as well as from the electrode. With the dental drill a bone flap of 5 x 5 mm, having the cobalt hole in its center, was isolated. All cobalt-gelatin material was removed both from the dura and the bone flap. The dura was opened while the cortex was constantly moistened with sterile saline at body temperature. A dissecting microscope was

used to make four subpial transections 2 mm deep at a length of 2.5 mm each, forming a square of 2 x 2 mm around the focus. The cuts were made with an ophthalmic knife or with a dental instrument which was bent in the desired shape and had a sharpened blade. Usually only two insertion points were needed to make the four incisions.

Under the microscope the upper edge of the knife could be followed on its route under the pial blood vessels. When the bleeding stopped, the cortex was covered with dura which was sutured with 6-0 ophthalmic suture. The bone flap was replaced and stabilized with acrylic. After the original electrode was again inserted in the center hole and covered with dental-cement, the sinus was closed and the skin sutured around the mold.

The procedure as described here was slightly changed in some experiments where seven screws were used: one ground, two occipital, two parietal and two as close as possible behind the focus. No special electrodes, as described previously, were placed over the focus and the homotopic region. The sham operations did not differ from the usual second operation except that no subpial transections were made.

Special care was taken to remove all the cobalt-gelatin material and to expose the cortex to the air as long as in the original operations.

ii. Recording

The electrocorticograms, recorded by a model 6 Grass electroencephalograph with eight channels, were done on unrestrained cats. A shielded microdot cable connected the headplug with the poly-

graph jack box. Both bipolar and unipolar recordings were made, using the ground screw as the indifferent electrode. The paper speed was 30 mm/sec while the high frequency filter was set at 70 and the time constant at 0.12 or 0.05 sec. An amplification factor of 7.5 μv/mm was always used but in some cases the sensitivity was lowered with one third per step in all channels. Before each recording several calibration signals were produced and the impedance of the individual electrodes was registered. The 60 cycles filter was very rarely used.

iii. Stimulation

At several occasions photic stimulation was performed with a Grass photostimulator (model PS2). The cat was placed in a dark room and different flash frequencies were tested. In other cases intramuscular injections of 25 or 50 mg Metrazol (pentylenetetrazol) were made to provoke epileptic activity. Intravenous injections of Metrazol were also done using a Harvard infusion pump, Model 901 and a special cage was built to allow injections on unanaesthetized cats.

iv. Histology

The cats were killed with an intravenous overdose of sodium pentobarbital, followed by immediate intracardiac perfusion with saline and 10% formalin. A drawing was made of the brains, which were later sectioned serially at 7μ. Every fiftieth section was stained with the Weil-Weigert method or the Klüver-Barera method.

v. Behavioural testing

The aim of our experiments was not only to prove that subpial incisions are effective in neutralizing a spike focus, but also to demonstrate that such incisions result in no significant functional deficit.

Sperry (130) showed that multiple intersecting subpial cuts in the sensorimotor arm field of monkeys had a negligible effect on motor coordination. However, no precise information was given as to the "large variety of natural cage and special test performances" which were observed.

In cats several attempts were made to determine the effects of unilateral lesions in sensorimotor cortex on manipulation by cats (6, 45, 53, 69). Large lesions result in obvious changes in tactile placing and hopping reactions, locomotion and postural tonus. But smaller lesions are more difficult to demonstrate. One way to resolve the problem is based on the fact that ablation of the somatic sensory and motor areas of the cortex abolishes preoperative preferences for the use of the contralateral paw in manipulation. Forward et al. (45) and Warren et al. (151) described a series of tests to determine the paw preferences of cats. From their results they concluded that the interhemispheric inequality responsible for paw preference is restricted to the cortical representation of the forepaw in the dominant hemisphere. Especially the tasks which required more complicated manipulation (i.e. bottle test) were effective in transferring the preference to the preoperatively non-dominant paw. Therefore we selected two tests with a high degree

of difficulty: the bottle test and the lift test.

In the bottle test, a piece of food was placed in one of three plastic test tubes, 3, 2.5 and 1.5 inches in diameter and 7 inches long, lying horizontally with one opening towards the cat and the other towards the experimenter. The food was visible through the plastic screen on which the tubes were attached.

In the lift test, the cat had to take its paw through a 1.5 inch wide hole in a transparent plastic screen and lift the food 1.5 inches to bring it into his cage.

Each cat was given 50 trials daily on one test or the other (or both). When after several days the paw preference was clearly established, the cats were operated upon and immediately following recovery from the anaesthetic, testing was resumed. Three cats were used as controls.

A topectomy was performed on two cats one day following cobalt-gelatin application epidurally. In one case suction was used, in the other coagulation. One other cat underwent a partial coagulation of the motor cortex, but this cat was not rendered previously epileptic.

Table 1

COBALT-GELATIN APPLICATION (24 CATS)

Group	Cat	Pre-Op Jerks	Pre-Op Spikes	Days between 1st. & 2nd. Op	Post-Op Jerks	Post-Op Spikes
Extradural	215					
	219					
	114					
	230					
Epidural	224			7		
A. Sham	14	−	+	3	−	+
	17	+	+	1	−	+
	12	−	+	1	−	+
	83	+	+	1	+	Electrode Defect
	82	−	+	1	−	+
B. Subpial	259			15		
	234			3		
	233			3		
	242	−	+	3	−	−
	49	+	−	3	−	−
	19	−	+	1	−	−
	15	−	+	1	−	−
	59	+	+	1	−	−
	285	−	+	1	−	−
	(267)			(4)		
Subdural A. Control	275	−	+			
	5	−	+			
B. Subpial	16	+	+	1	−	−
	50	−	+	1	−	(−)

VI. RESULTS

Although the preparations with aluminum hydroxide and cobalt powder were not used to test the effects of subpial transection, we will consider them briefly.

A. Aluminum Hydroxide

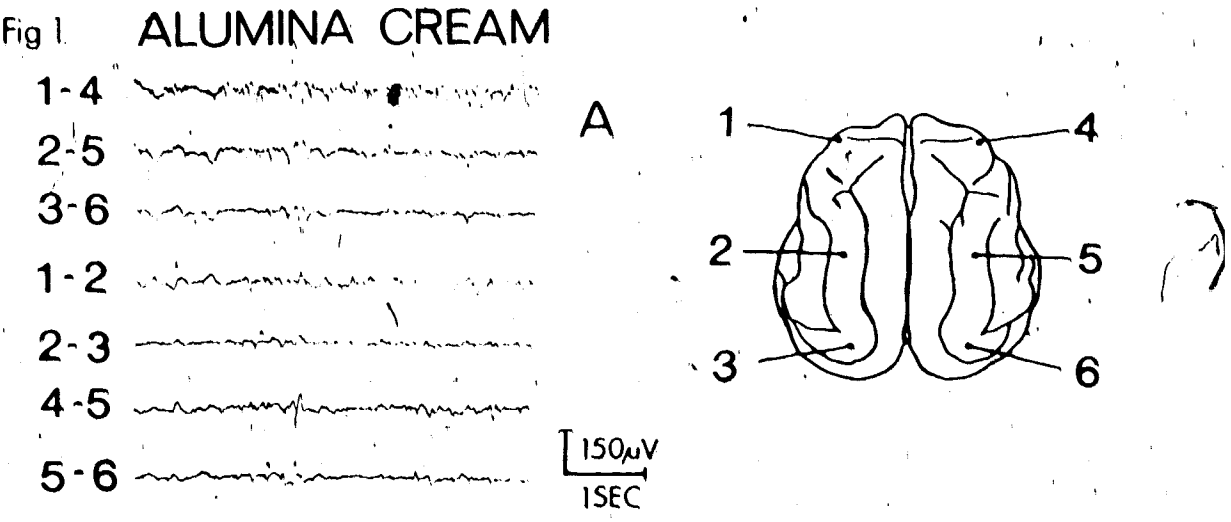
In the Amphogel group, only one cat showed EEG signs of epilepsy. In this cat (No. 10), the chemical was injected in the left motor cortex and ipsilateral abnormalities could be seen 28 days following surgery. The dysrhythmia remained for 14 days.

The three alumina cream cats did not develop a clearcut focus. Occasionally spikes were seen ipsi- or heterolaterally, but there was no consistent spike focus (Fig. 1A).

B. Cobalt Powder

The four cats in this group all became epileptic, the degree of abnormality depending on the size of the lesion. The cat which received 50 mg on the left motor cortex showed clonus of the right forepaw for 3 days, corresponding with a left frontal spike focus (Fig. 1B). Later 4 cycles/sec spike- and wave-type activity and dysrhythmic patterns were seen over the left hemisphere, lasting for about 20 days postoperatively. Cat 142 received 75 mg cobalt on the left motor cortex and died after a period of 4 days, during which time he developed a severe hemiparalysis and had several motor seizures. The other two cats who received 25 mg also showed motor seizures, but

Fig 1


ALUMINA CREAM
1-4
2-5
3-6
1-2
2-3
4-5
5-6
A
150μV
1SEC
1
4
2
5
3
6
COBALT POWDER
1-4
2-5
3-6
1-2
2-3
4-5
5-6
B
100μV
1SEC
COBALT EXTRADURAL
1-4
2-5
3-6
1-2
2-3
4-5
5-6
C
150μV
1SEC

only during the first postoperative day. Photic stimulation did not provoke epileptic activity in this series of cats, nor in the groups with aluminum hydroxide or cobalt-gelatin.

C. Cobalt-Gelatin

i. Extradural

This group included four cats. No changes were seen in one cat, while the other three presented non-specific abnormalities. The best results were obtained in cat 219 which received cobalt over the right motor cortex. The nearest electrode was 2 mm behind the lesion. In this cat bilateral and unilateral spikes were seen 8 days after the operation. The hypersynchronization lasted for 6 days (Fig. 1C). In another cat (230) sharp activity and dysrhythmic waves were recorded up to 5 weeks after the operation. Again, no well defined focus could be detected.

ii. Epidural

This series of 16 cats was by far the most useful. The cobalt-gelatin was pushed through a small hole in the skull overlying the dominant motor cortex. However, some variability arose because it was only possible to visually control the exact amount of material sitting on the dura in the second operation when the bone flap was removed. It turned out that a larger amount of cobalt-gelatin was correlated with the appearance of both spikes and jerks, while smaller amounts resulted in only cortical spikes during 2 or more days following cobalt-gelatin application. In some cases (cats 82 and 242)

there was a delay of 2 or 3 days before the onset of spiking. However, this variability was present as well in the control group as in the experimental group and still a considerable difference was seen between these two groups.

Spiking and jerking persisted in those cats which received a sham-operation, while subpial incisions were able to stop both. Thus, simple removal of the cobalt-gelatin material from the dura does not result in a cease-fire of the focus.

A summary is given in Table 1 and an individual description will be given below.

a. Sham operations.

The control operations were done one day following the first surgery in three cats (12, 17, 83) while three other cats (1,4 82, 224) were operated upon after a period of 3 or more days.

Cat 12 (Fig. 2) showed spikes of $\pm$ 130 μV both in the record taken just prior to the sham operation and in the trace which was obtained one day after the sham operation. It can be seen on the second record that there is a phase reversal in the electrode behind the focus, but the amplitude of the spikes is virtually unchanged. Subsequent EcoG's revealed only minor changes at the site of the focus.

Cat 17 (Fig. 3) demonstrated jerking of the left forepaw one day following cobalt application to the right motor cortex. This was accompanied by spikes of $\pm$ 140 μV. Similar spikes, but without jerking, were seen in two recordings, respectively taken 8 hours (cat sleeping) and 24 hours (cat awake) after the sham operation.

Fig 2. Cat 12

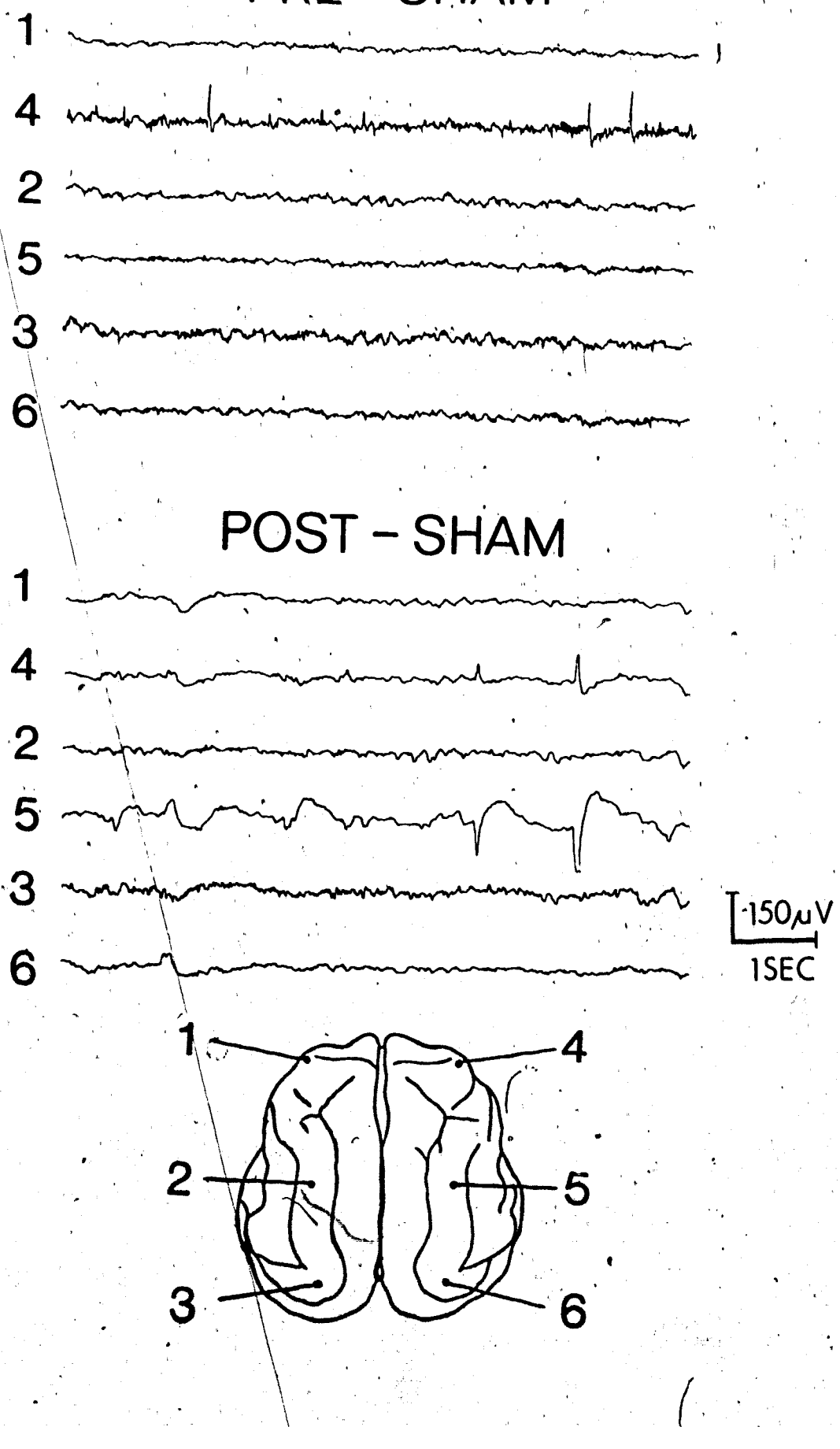
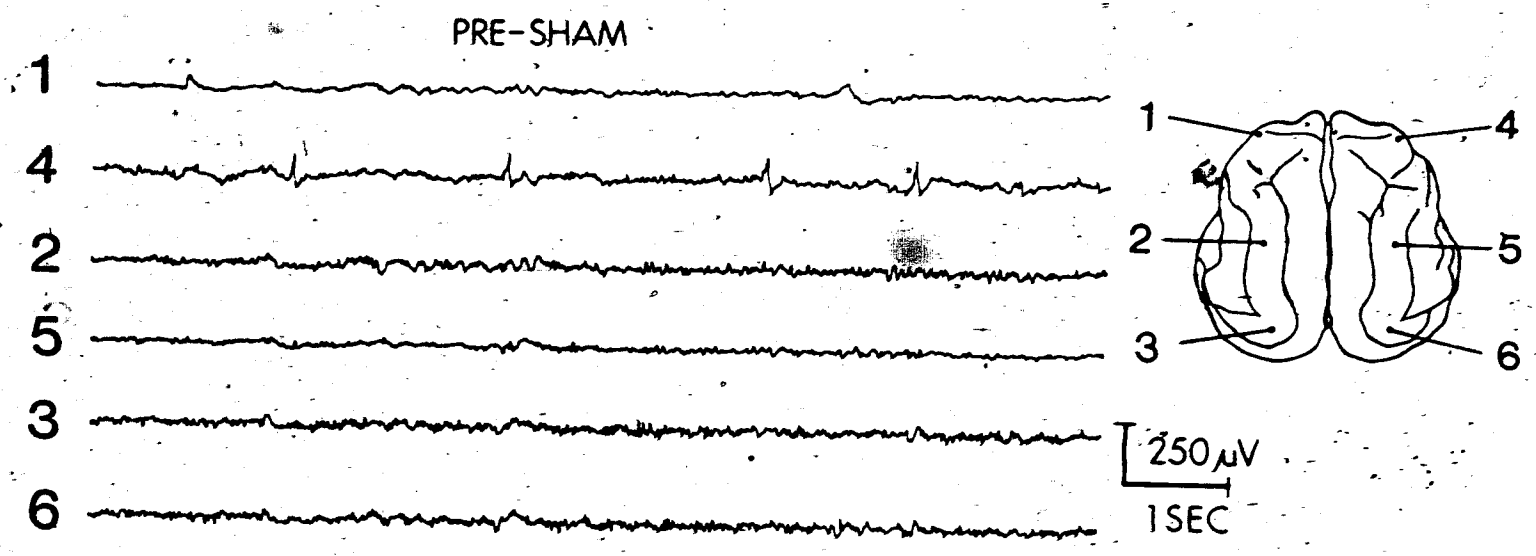


Fig 3. Cat 17


PRE-SHAM
1
4
2
5
3
6
250μV
1SEC
1
4
2
5
3
6
POST-SHAM
1
4
2
5
3
6
250μV
1SEC
1 DAY POST-SHAM
1
4
2
5
3
6
250μV
1SEC
3 DAYS POST-SHAM
1
4
2
5
3
6
150μV
1SEC

Paroxysmal events were observed as long as 3 days after the sham operation, but there was a marked reduction in the spike amplitude.

Cat 83, having spikes of 150 μV over the left motor cortex, jerked with its right forepaw prior to the sham operation. The bone flap over the focus broke during its removal and replacement of the concerned electrode was impossible. However, high amplitude spikes could be recorded in the electrode behind the focus on the same hemisphere and, more important, jerking of the right forepaw was observed 1 day after the sham operation.

Cat 82 presented 140 μV spikes, but only on the second day after the introduction of the epileptogenic agent. On the third day a sham operation was performed and 140 μV spikes could still be seen on a recording taken 12 hours later. The next day the spikes were predominant in the trace from the electrode behind the focus.

Cat 14 had spikes (150 μV) and jerks on the two days following the first operation. No jerks and only very few spikes were seen just prior to the sham operation on the third day. The recording taken afterwards revealed the existence of sharp activity simultaneous at the focus and at the electrode behind the focus.

Cat 224 showed a spike focus on the day following application of the cobalt-gelatin on the right motor cortex. This focus could be activated by slow intravenous injection of metrazol. A total of 53 mg/kg was injected and this resulted in two grand mal episodes, respectively at 30 and 60 minutes after the end of the injections. (Injection rate: 1, 94 cc/min, concentration: 3, 22 mg/cc). Ipsi- and heterolateral sharp activity remained for one week whereafter

a sham operation was performed. Following recovery, no changes were seen in the EcoG and the spikes (ipsilateral, dependent and independent heterolateral) remained for another 10 days.

In conclusion, isolated spikes with undiminished amplitude are recorded in the awake cat 1 day following the sham operation. However, it is important that both control and experimental operations are performed on the first or second day in the evolution of the focus. Otherwise the focal abnormality is extinguished before it is used in testing the effects of the operations. It is of interest to note that in one case (cat 83), motor seizures persisted after the sham operation.

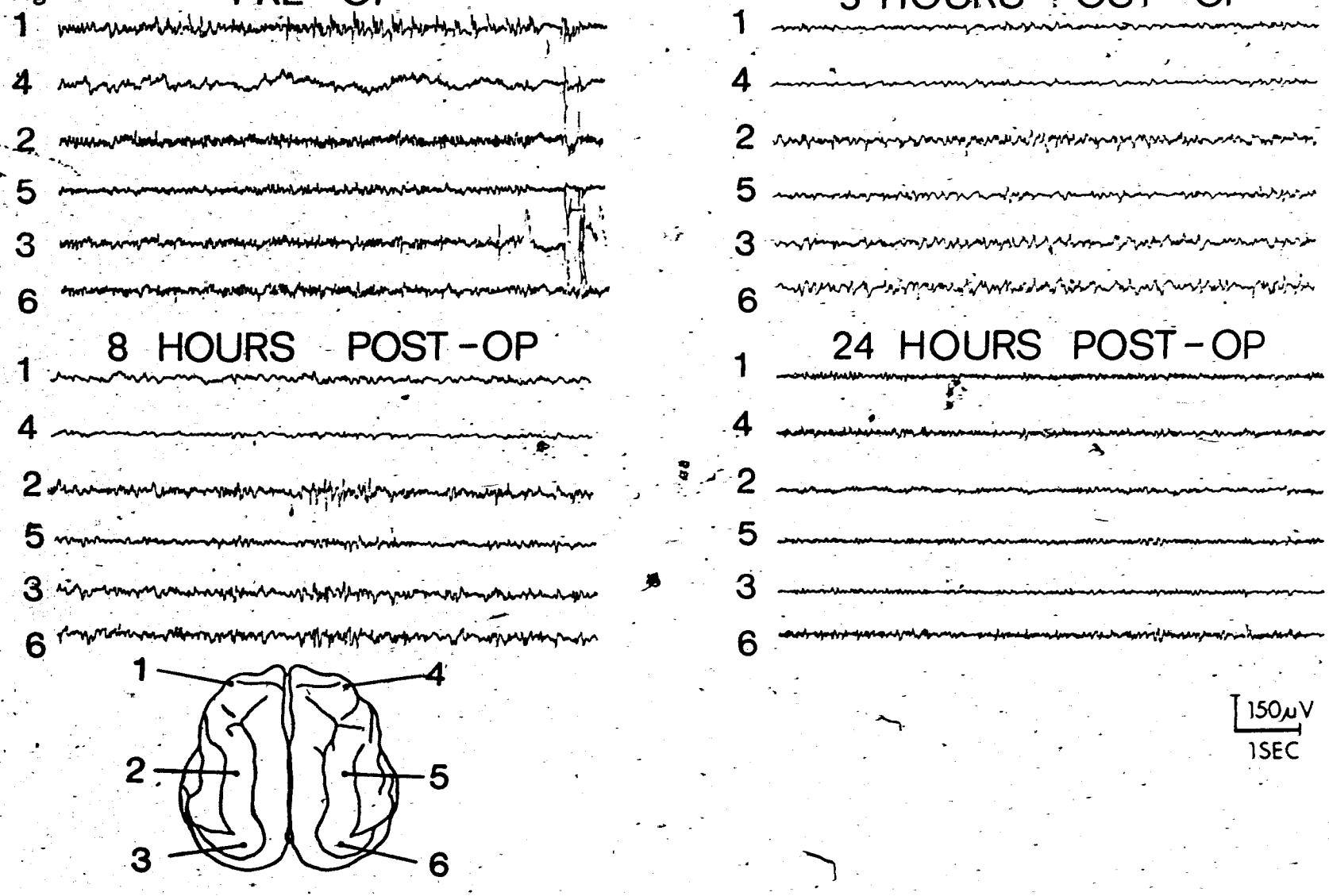
Some information is available concerning the evolution of the focus: in a first stage the abnormality is strictly confined to the focus while in a later stage the whole ipsilateral hemisphere is involved with a maximum spiking in the electrode behind the lesion.

b. Subpial transections

Again, some cats (19, 59, 15, 285) were operated on the day following the cobalt-gelatin application, and others (233, 242, 49, 234, 259) on a later date. Subpial transections around the epileptic area were very effective in preventing hypersynchronization of the focus in all animals. However, in some cases an ipsilateral hemisphere discharge could be seen postoperatively, indicating that the operation was not always successful in abolishing the second stage of the evolution of the focus. A more specific description will follow.

Cat 59 (Fig. 4) showed spike trains (140 μV) in association

Fig 4. Cat 59

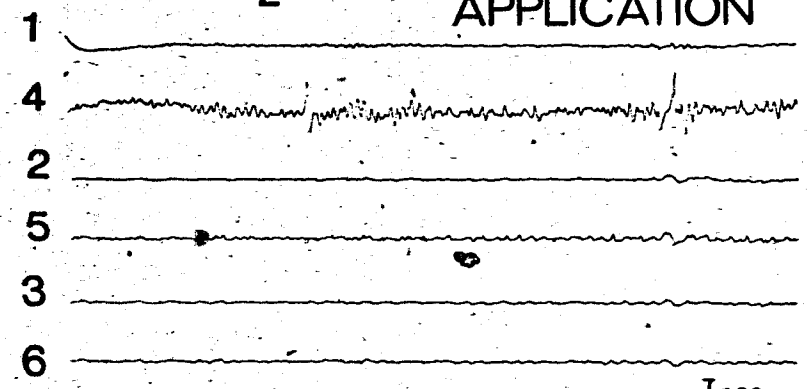

PRE-OP
1
4
2
5
3
6
8 HOURS POST-OP
1
4
2
5
3
6
3 HOURS POST-OP
1
4
2
5
3
6
24 HOURS POST-OP
1
4
2
5
3
6
150μV
1SEC
1
4
2
5
3
6

with right forepaw jerks prior to the operation. No such spikes or jerks were seen in the recordings taken 3 hours (cat sleeping) and 8 hours (cat awake) post-operatively. But in this last record one can observe rather sharp activity in the ipsilateral parietal electrode while the frontal leads remain silent. Further traces (one day or more post-operatively) were completely normal.

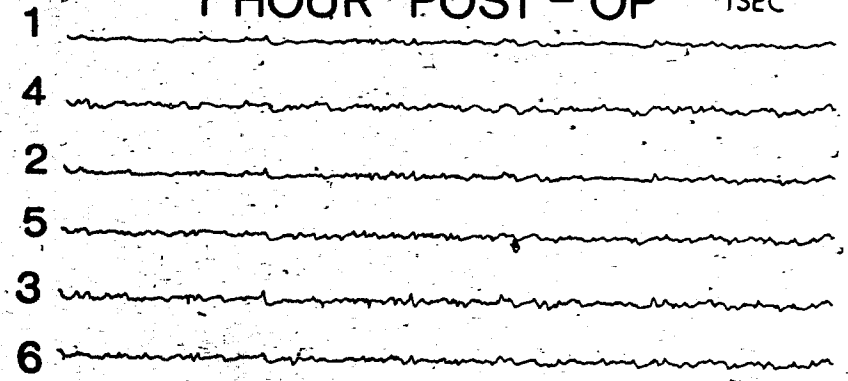
Cat 19 (Fig. 5) had single spikes (150 μV) 4 1/2 hours following cobalt-gelatin application. On the next day trains of small spikes (50 μV) were recorded prior to the operation. The post-operative EcoG was normal but 5 days later a train of very small spikes (20 μV) was seen. This train occurred only on one occasion and it is of interest to note that simultaneous spikes can be seen in the electrode behind the focus, suggesting a common thalamic origin.

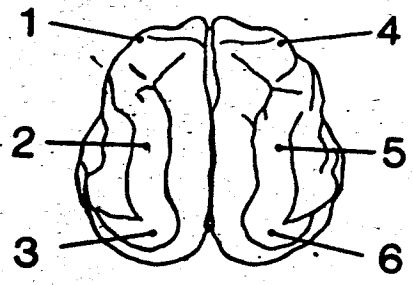
Cat 15 (Fig. 6) presented 50 μV spikes 1 day after the first operation. The record taken 1 hour after the subpial transection revealed a left hemisphere discharge with maximum negativity in a location between the parietal and the occipital electrode. The next day a sleep recording was obtained with a great number of spindles. Sharp spindle-like activity was also seen over the left frontal area, but isolated spikes were hard to detect. Moreover, in a subsequent EcoG taken on the same day but with the cat awake there were no spikes at all. This illustrates the important influence of the level of consciousness on the behaviour of the focus. It was noticed in several cats that spindle-like activity over the epileptic area appeared in the recordings taken while the cat was still sleeping

Fig 5. Cat 19 4½ HOURS AFTER CO APPLICATION

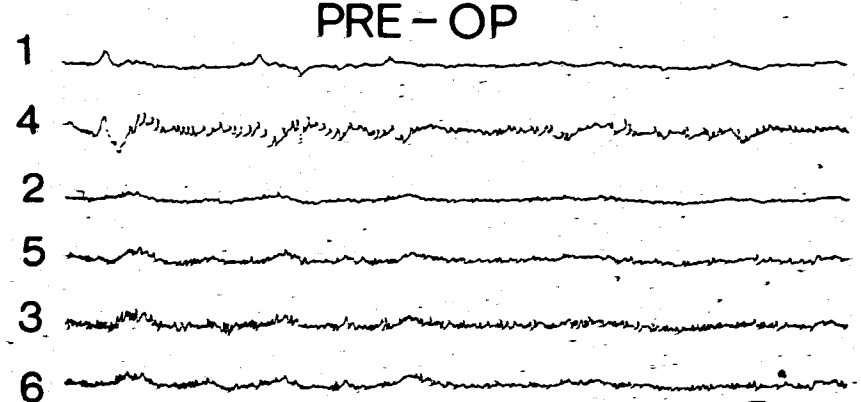


1 HOUR POST-OP





PRE-OP



5 DAYS POST-OP

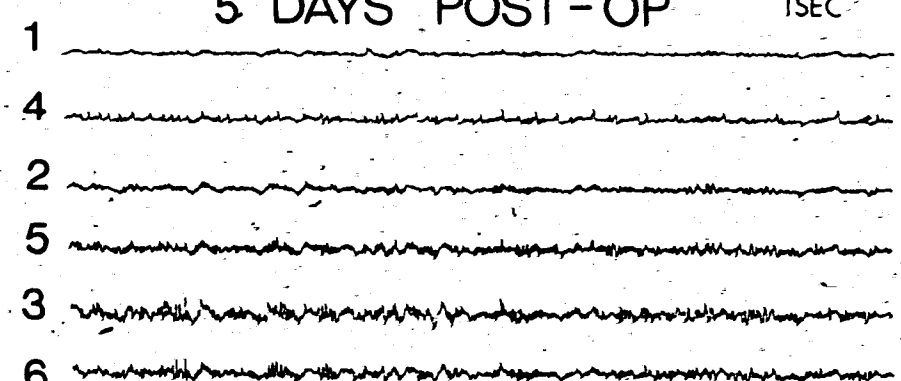


Fig 6. Cat 15

PRE-OP

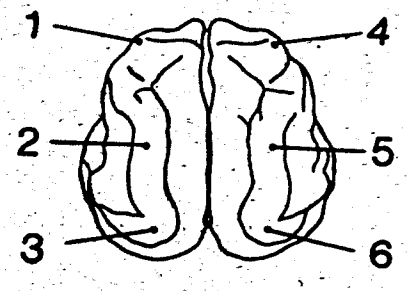
1
4
2
5
3
6

100μV
1SEC

1 DAY POST-OP

1
4
2
5
3
6

250μV
1SEC



1 HOUR POST-OP

1
4
2
5
3
6

150μV
1SEC

1 DAY POST-OP

1
4
2
5
3
6

250μV
1SEC

under the effect of the anaesthetic. However, isolated spikes were never seen over the transected region once the cats were recovered from the anaesthetic.

Cat 285 (Fig. 7) is another example of this phenomenon. In the recording taken 2 hours post-operatively, spindles are seen in the frontal leads, although in this case fewer spindles are seen over the transected area than over the heterolateral region. Two days later abnormal sharp activity appears over the right hemisphere with a predominant abnormality in the region behind the previous focus. Later recordings were normal.

Considering these four cats which received subpial transections on the day following the creation of the focus, one can summarize the results by saying that isolated spikes are no longer seen over the previously epileptic area once the cats recovered from the anaesthetic.

This is quite different from what is seen in the sham operated cats, where individual spikes were recorded on the day following the control operations.

We will now report on a few more cats which received subpial incisions several days after the application of the cobalt-gelatin.

Cat 49 (Fig. 8) was almost constantly jerking with its left forepaw for the first 3 days after the first operation. However, spikes were only seen on the EcoG of the first post-operative day, very rarely on the second day, and not at all on the third day. The subpial transections were done on the third day and as a result the jerking stopped. Subsequent EcoG's were normal. It is evident that

Fig 7 Cat 285

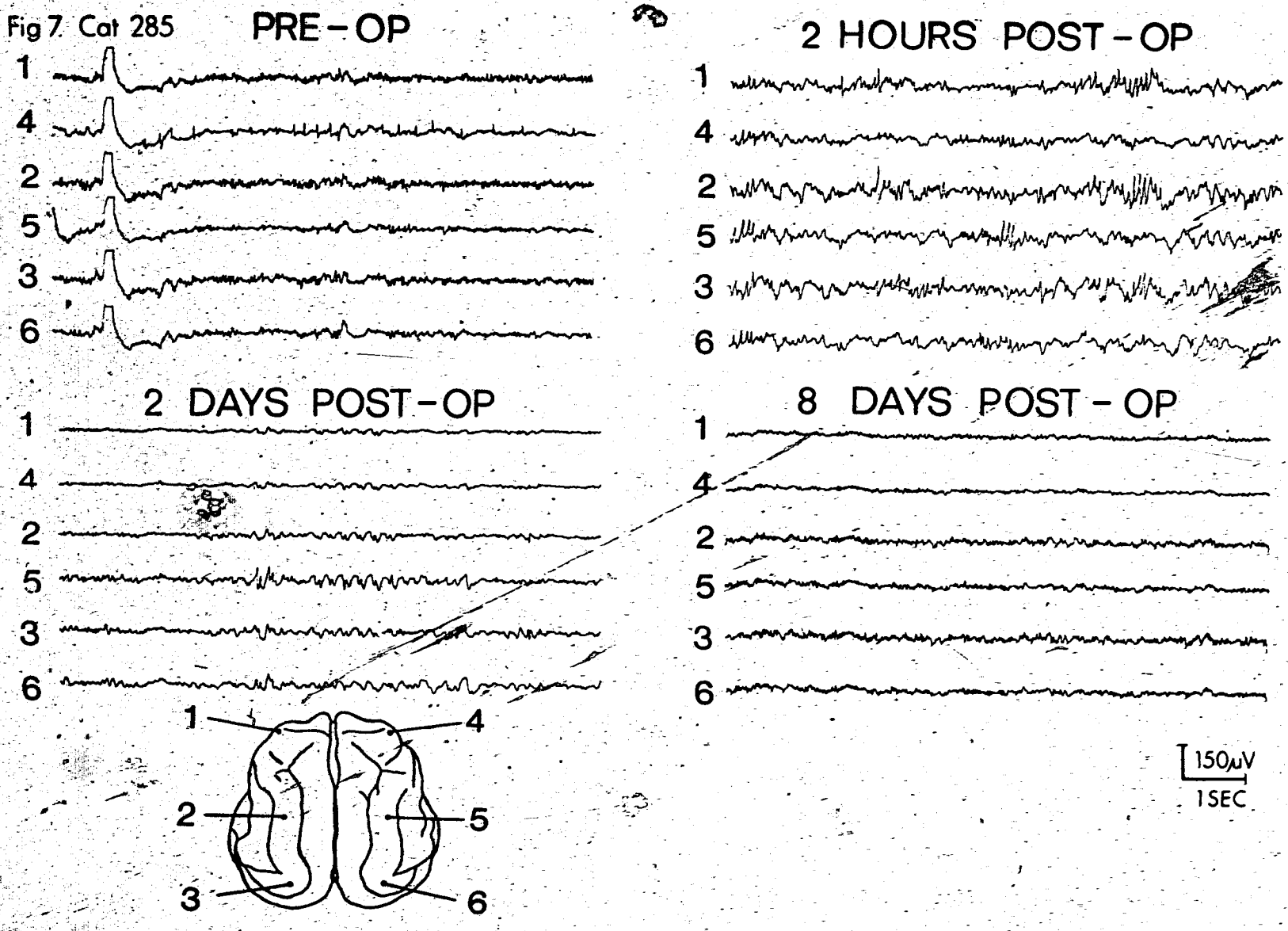

PRE-OP
1
4
2
5
3
6
2 HOURS POST-OP
1
4
2
5
3
6
2 DAYS POST-OP
1
4
2
5
3
6
8 DAYS POST-OP
1
4
2
5
3
6
150μV
1SEC
1
4
2
5
3
6

Fig 8. Cat 49

1 DAY AFTER CO APPLICATION

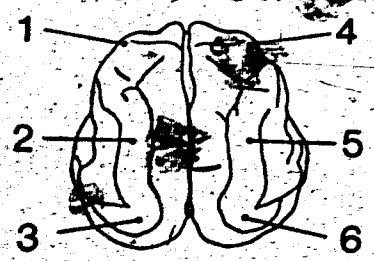
4
1-4
2-5
3-6
1-2
2-3
4-5

2 DAYS AFTER CO APPLICATION

1-4
1
4
2
5
3
6

3 DAYS AFTER CO APPLICATION

1
4
2
5
3
6



8 HOURS POST-OP

1
4
2
5
3
6

this cat was an exception in every respect. No other cat in the epidural series had jerks up to 3 days after the cobalt-gelatin application and no other cat had such a short-living spike focus. Histological examination provided no explanation for this unusual phenomenon.

Cat 242 (Fig. 9) developed a spike focus after a delay of 2 days. Following recording of these high amplitude (200 μV) spikes, an operation with subpial transections was performed. Subsequently, no spikes were seen over the transected area but paroxysmal events were recorded in the electrodes behind the lesion. Up to more than 1 month after the subpial transection it was possible to observe dysrhythmic patterns over the ipsilateral hemisphere, while the frontal leads showed virtually no involvement.

Cats 233, 234, and 259 are of less importance since the electrode which was nearest to the focus was at a distance of 2 to 3 mm. Subpial transections were made on the third post-operative day (cats 233, 234) or in one case (cat 259) on the fifteenth day.

Cat 233 had a very discrete focus which only fired when metrazol was slowly injected intravenously. The subpial incisions on this cat failed because the pia ruptured, causing extensive bleeding and an electrical "delta" focus. Cats 234 (Fig. 10) and 259 were mainly of interest because of the information concerning the evolution of this epileptic model. In both cats a hyperactivity was noticed in the electrodes behind the lesion after a period of 2 weeks. A dysrhythmia of the ipsilateral hemisphere, previously described as the second stage in the evolution of the cobalt-gelatin

Fig 9. Cat 242

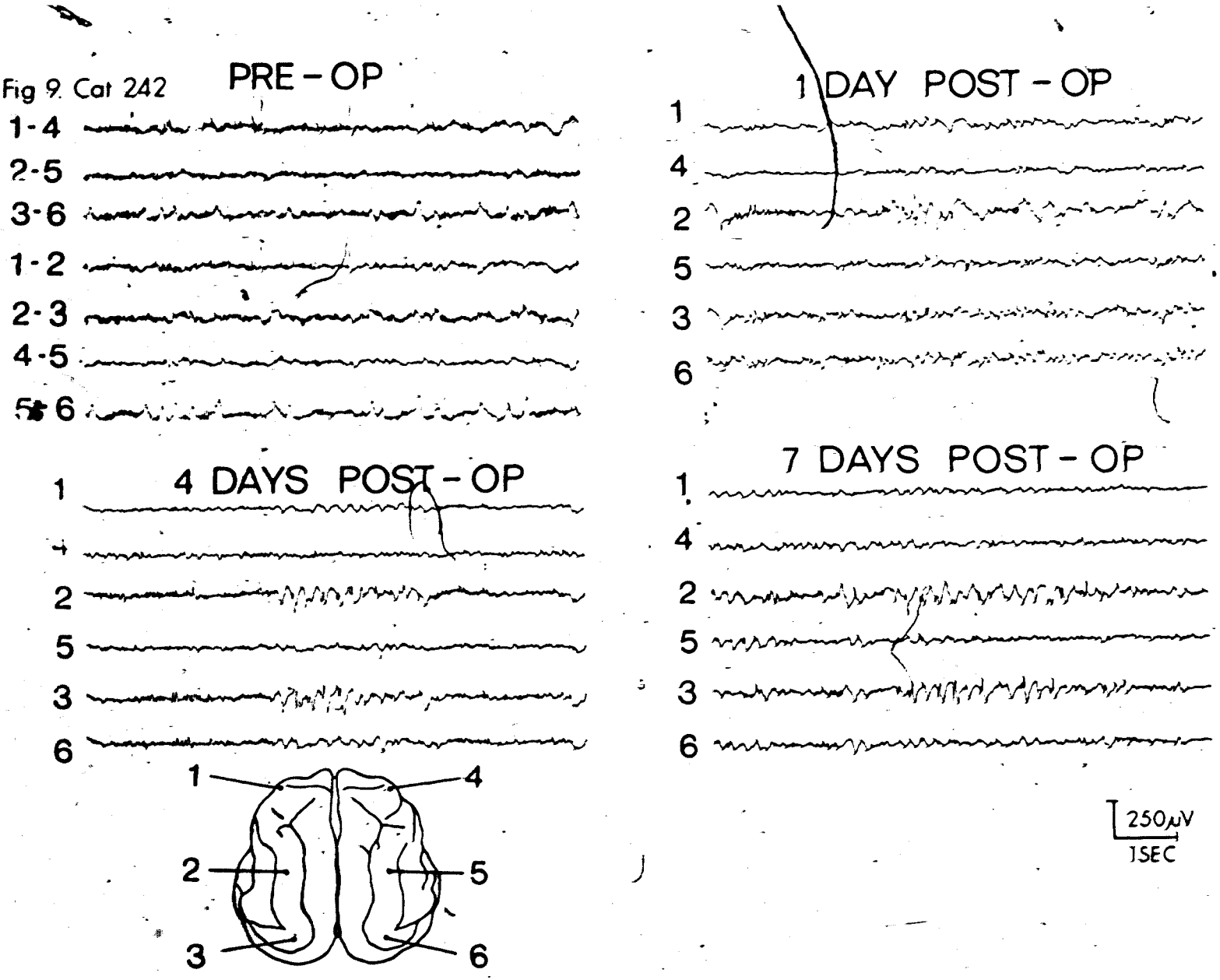
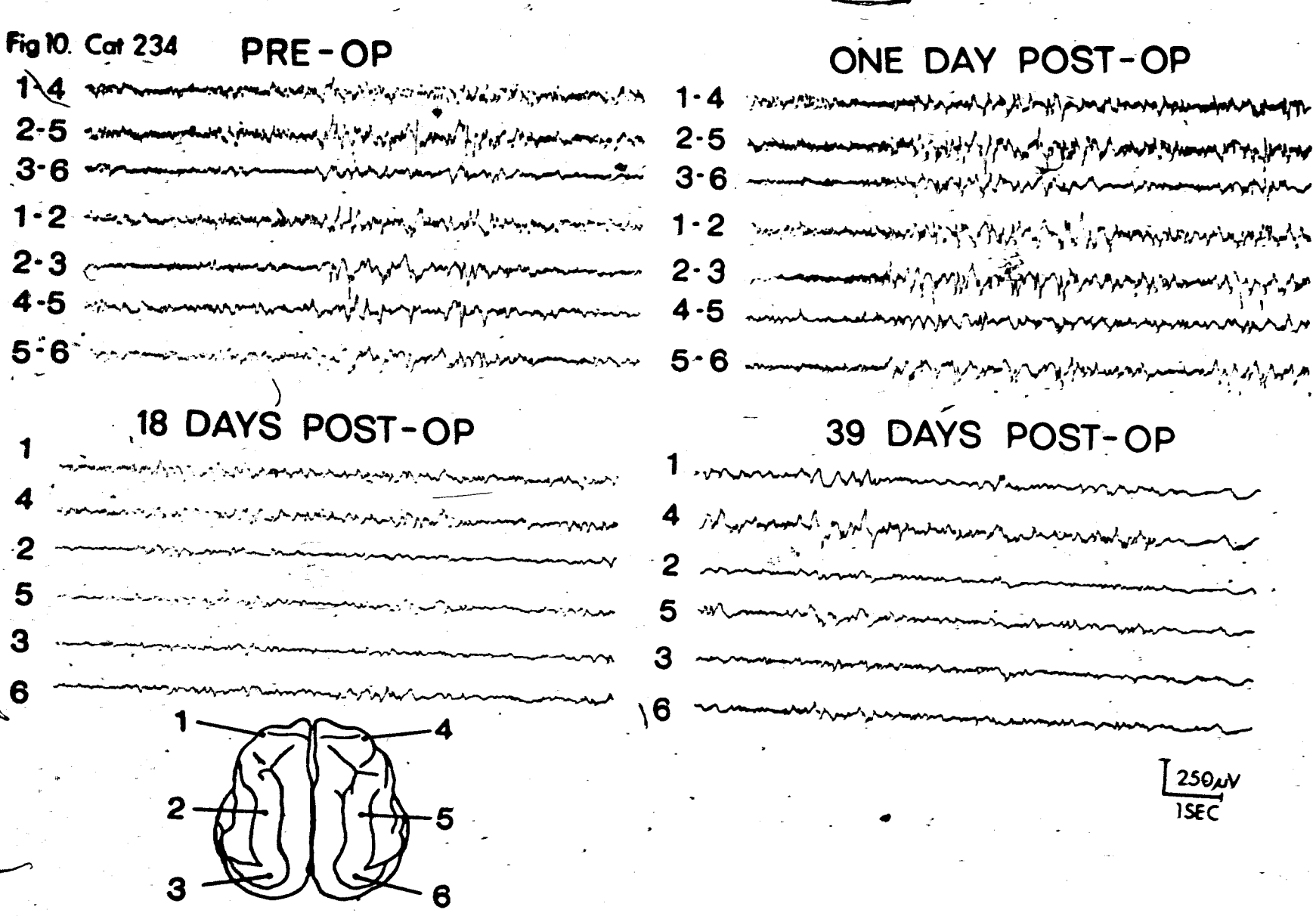

PRE - OP
1-4
2-5
3-6
1-2
2-3
4-5
5-6
4 DAYS POST - OP
1
4
2
5
3
6
1 DAY POST - OP
1
4
2
5
3
6
7 DAYS POST - OP
1
4
2
5
3
6
250μV
1SEC

Fig 10. Cat 234



focus, was seen up to 90 days post-operatively.

In conclusion, in those cats which were operated upon after a period of 3 or more days, there is a much larger "second stage". Apparently, the longer delay gave the focus a bigger chance to influence other structures. Finally, it is worthwhile to mention Cat 267 which had first subpial incisions over the left motor cortex and 3 days later received cobalt-gelatin over the same area. No isolated spikes were observed over the transected region as a result of the cobalt application. Instead, left hemisphere discharges were seen with components in the frontal lead during the first 3 days after the placement of the epileptogenic material. One week later the recording was normal except for an accentuation of the 14 cps background at the electrode overlying the transected area.

The findings in this epidural group are summarized in the following points:

1. Individual spikes at a cobalt-gelatin focus do not disappear after a sham operation but isolation of the epileptic area with vertical cortical subpial incisions was very effective in abolishing this type of hypersynchronization.
2. The subpial isolation had no effect on rhythmic phenomena such as spindles. Discharges involving the whole hemisphere simultaneously were also reflected in the transected area, although the amplitude of this activity seemed reduced at this site.

3. The evolution of the epidural cobalt-gelatin focus can be described in two stages. In the first stage, lasting for 2 or 3 days, there are isolated spikes, ranging from 50 to 200 μV, and trains of spikes confined to the epileptic focus. In the second stage, the abnormality is spread over the ipsilateral hemisphere. The appearance of the second stage is determined by the delay between the creation of the focus and the removal of the epileptic material. The longer this delay, the more chance there is that the second stage develops.

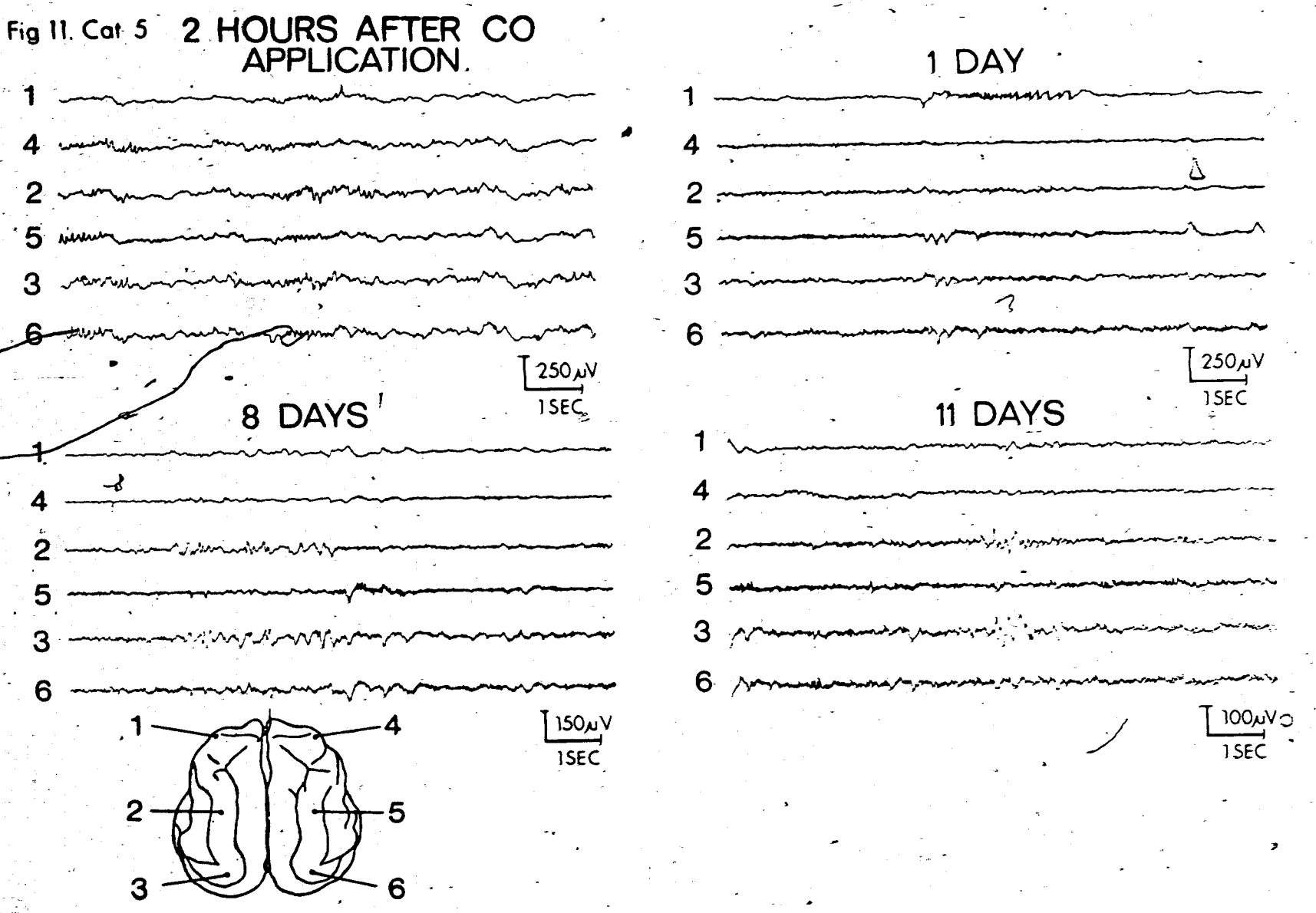
iii. Subdural

On four cats the cobalt-gelatin was placed subdurally. Two of them had subpial surgery on the following day (Cats 5, 16), while the other two (Cats 275, 50) received no second operation.

Cat 5 (Fig. 11) served as a control. The evolution of the focus was somewhat similar to what was described for the epidural group. Two hours after the cobalt implantation, hypersynchronous activity was seen over the focus. One day later, spike-wave trains were recorded and subsequent EcoG's revealed left hemisphere discharges.

Cat 275 presented somewhat unreliable results since the cobalt-gelatin sat much deeper in the cortex than in the other three cats. Spiking was recorded up to 7 days following the creation of the focus.

Fig 11. Cat 5


2 HOURS AFTER CO APPLICATION.
1
4
2
5
3
6
250μV
1SEC
8 DAYS
1
4
2
5
3
6
150μV
1SEC
1
4
2
5
3
6
1 DAY
1
4
2
5
3
6
250μV
1SEC
11 DAYS
1
4
2
5
3
6
100μV
1SEC

Cat 16 (Fig. 12) showed long trains of spikes and jerking of the right forepaw on the first day after the cobalt application. Subpial transections were made on the same day and recording was resumed 5 hours post-operatively. No jerks were observed and the sleep trace was characterized by ipsilateral hemisphere discharges and spindles which were reflected at the electrode overlying the transected area. Later recordings revealed left hemisphere discharges but the frontal lead showed no abnormalities.

Cat 50 was comparable to the previously described cat. Spikes were seen 1 day after the cobalt-gelatin application. A recording taken after the subpial surgery on the same day showed generalized left hemisphere spikes. However, later recordings could not be obtained since the cat died of an overdose of anaesthetic.

This group is too small to allow relevant interpretation. However, one can at least notice that the evolution of the focus presents similarities with the epidural group. Involvement of the ipsilateral hemisphere is more likely to occur since the epileptogenic material is in more direct contact with the brain. In one cat (Cat 16) it was possible to stop both focal spikes and jerks with subpial isolation of the focus 1 day after the application of the cobalt-gelatin.

iv. Behavioural testing

Paw preference testing was performed on a total of 25 cats. Some of the results are summarized in Table 2. All the cats which received subpial transections were tested post-operatively on their

Fig 12. Cat 16

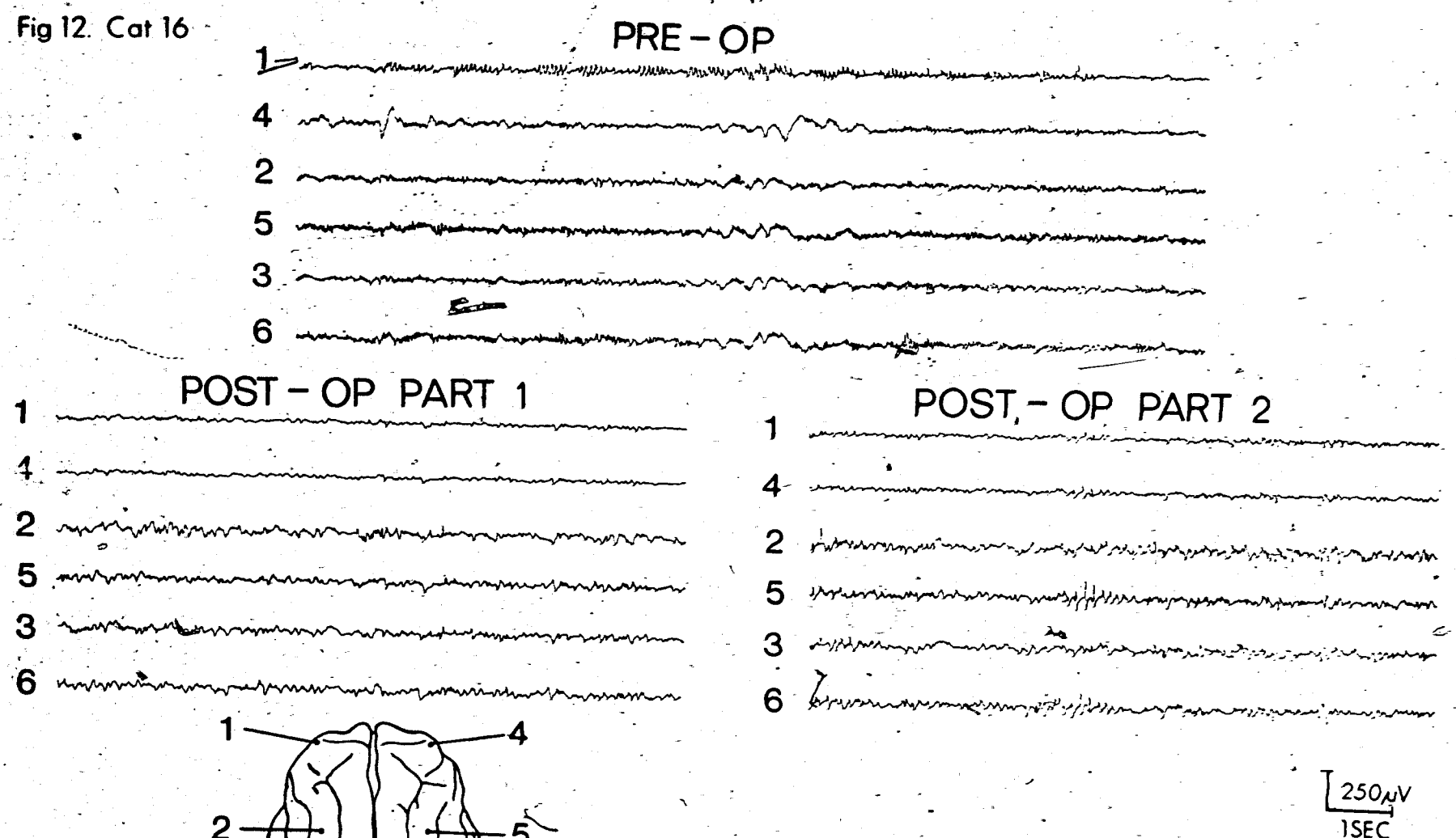

PRE - OP
1
4
2
5
3
6
POST - OP PART 1
1
4
2
5
3
6
POST - OP PART 2
1
4
2
5
3
6
250μV
1SEC
1
4
2
5
3
6

Table 2

USE OF PREFERRED PAW ON 50 TRIALS ON THE BOTTLE TEST

Group	Pre-Op	Post-Op	t-ratio
Subpial Transections			
Cat 285 (epidural)	39 33 37	38 41	t = 1.248 (P = 0.50)
Cat 16 (Subdural)	45 46 45	49 44	t = 0.339 (P < 0.50)
Topectomy			
Cat 26 (not effective)	40 44 45 43	43 41 44 46	t = 0.333 (P < 0.50)
Cat 65 (effective)	38 30 27 26	7 5 6 5	t = 9.262 (P = 0.01)
Coagulation			
Cat 432 (coag. non dominant motor cortex)	31 31 27 37 32	37 43 39 43 41 39 30	t = 3.903 (P = 0.01)

placing and hopping reflexes and their gait was observed. No deficits could be detected and the results on the bottle or the lift test showed no significant differences (see Cats 285 and 16 in Table 2).

To control these results we performed a topectomy (removal of epileptic brain tissue) on two cats. Cat 26 was operated upon 1 day after the epidural application of cobalt-gelatin. However, coagulation of the epileptic area was too conservative: focal spikes could still be seen 2 days after the topectomy and there was no significant difference in the use of the preferred forepaw. Therefore, a more extensive removal of the epileptic area, using suction, was tried on Cat 65. Spikes and jerks disappeared and there was almost a complete reversal of the paw preference.

Finally, a non-epileptic cat (432) was used to test the hypothesis that coagulation of a part of the non-dominant motor area would result in a reinforcement of the paw preference. As seen in Table 2, there was in fact a significant increase in the use of the preferred paw.

Further evidence is needed to prove that paw preference testing is sensitive enough to reveal functional motor deficits, but at least these experiments strongly indicate that subpial transection of the forepaw motor area causes far less functional damage than a topectomy of the same area. Indeed, a topectomy which is extensive enough to destroy a spike generating focus causes paralysis of the heterolateral forepaw and a reversal of the paw preference.

v. Histology

The morphology of alumina cream lesions in the motor cortex of the cat has been extensively studied by Velasco et al. (144). They found that injection of 0.03 ml alumina cream resulted in a lesion with a length of 1.5 mm. This is in agreement with our findings (Plate 1). However, the clinical symptoms as reported by Velasco et al. (144) were not observed in our series. The EEG of the cat from which Plate 1 was taken is illustrated in Fig. 1A.

The application of cobalt powder to the cortical surface results in a large crater-like lesion, characterized by loss of neurons and inflammatory reaction (Plate 2).

Far different are the lesions produced by small amounts of cobalt-gelatin. Sometimes the cortical epileptic area was not detectable visually during the operation and its location could only be determined by inspection of the overlying dura. In other cases it was possible to localize the focus by its paler appearance under the dissecting microscope. Minor abnormalities in the pial vascularization also provided a clue. Plates 3 and 4, both taken from cats with a sham operation, illustrate the morphology of a cobalt-gelatin lesion. It can be seen in Plate 4 that the abnormalities were confined to the molecular layer, while Plate 3 shows a more extensive lesion with inflammatory reaction.

The histological verification of the subpial incisions revealed that most cuts did not disrupt subcortical connections. However, some transections caused a more pronounced bleeding than others. In Plate 5 there is hardly any damage around the cuts, while

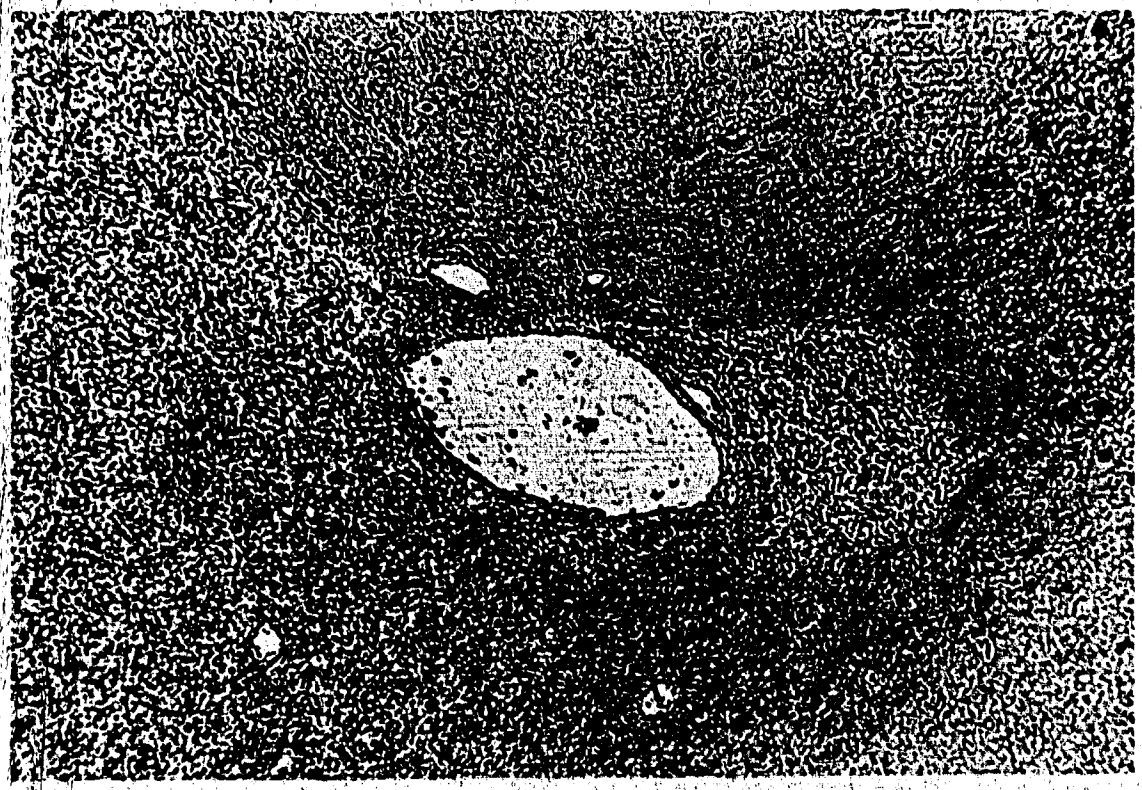


Plate 1. Photomicrograph of lesion produced by injection of 0.03 ml Alumina Cream in the cortex of Cat 184. Weil-Weigert method; 31 x.

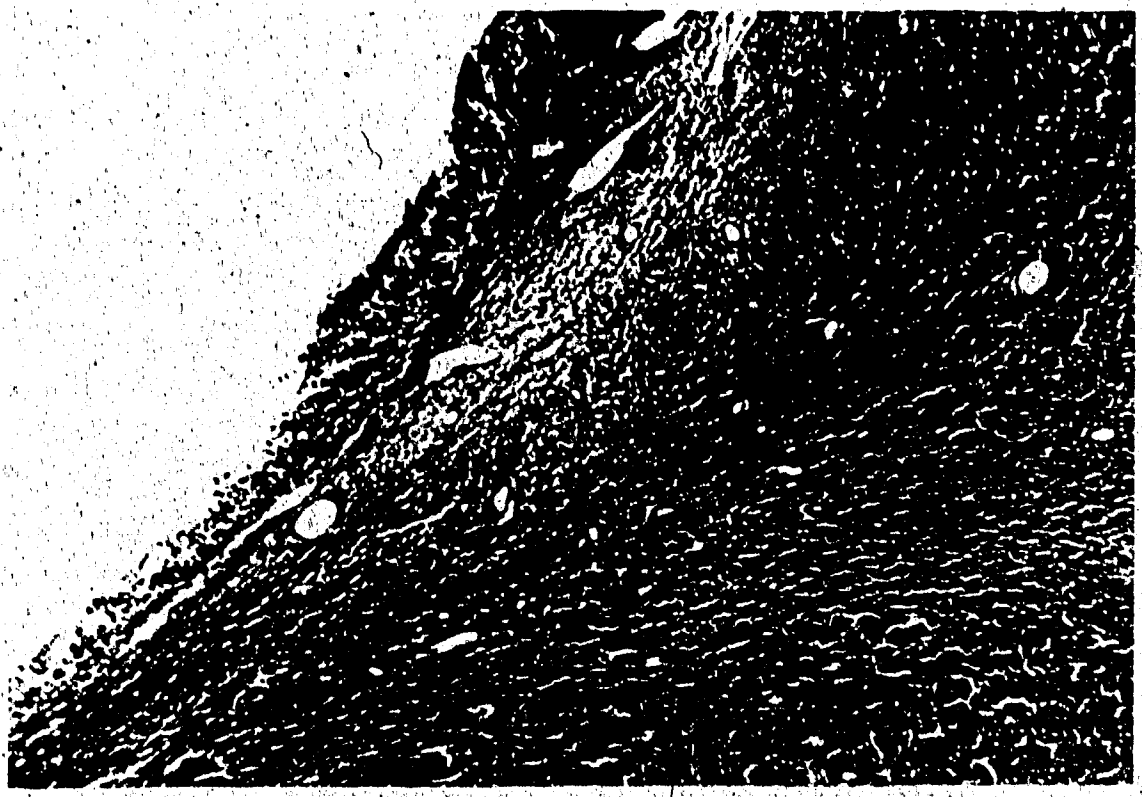


Plate 2. Cobalt powder lesion in Cat 142. Klüver-Barbera method; 31 x.

Plate 3. Lesion caused by epidural application of cobalt-gelatin on Cat 179. Weil-Weigert method; 31 x.

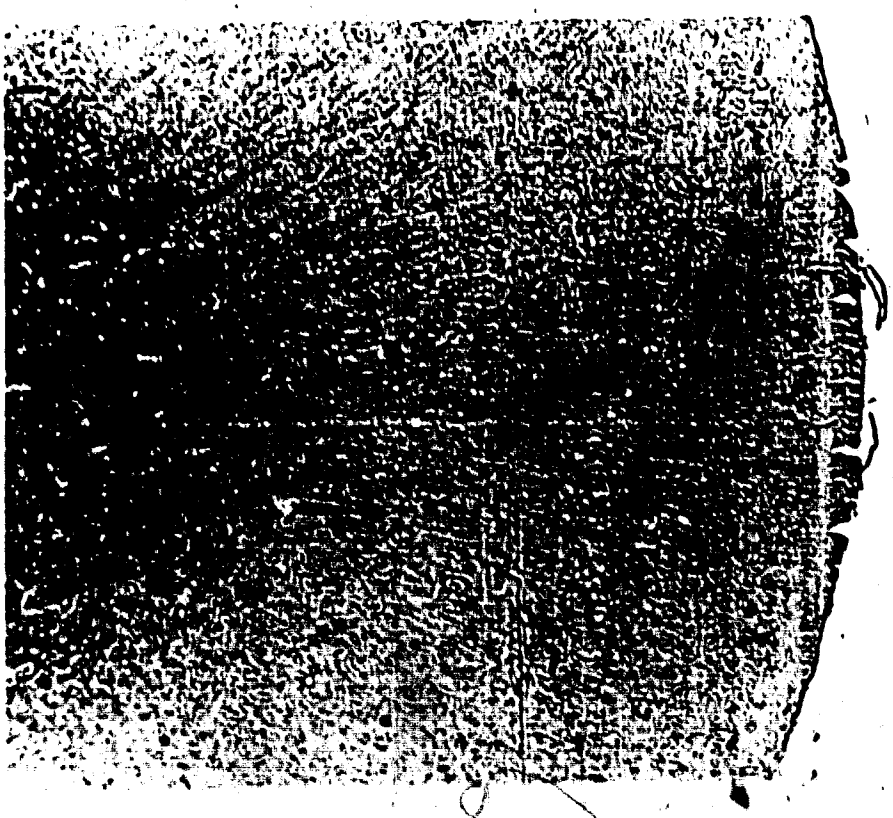


Plate 4. Similar but smaller lesion. Cat 12. Weil-Weigert method; 31 x.

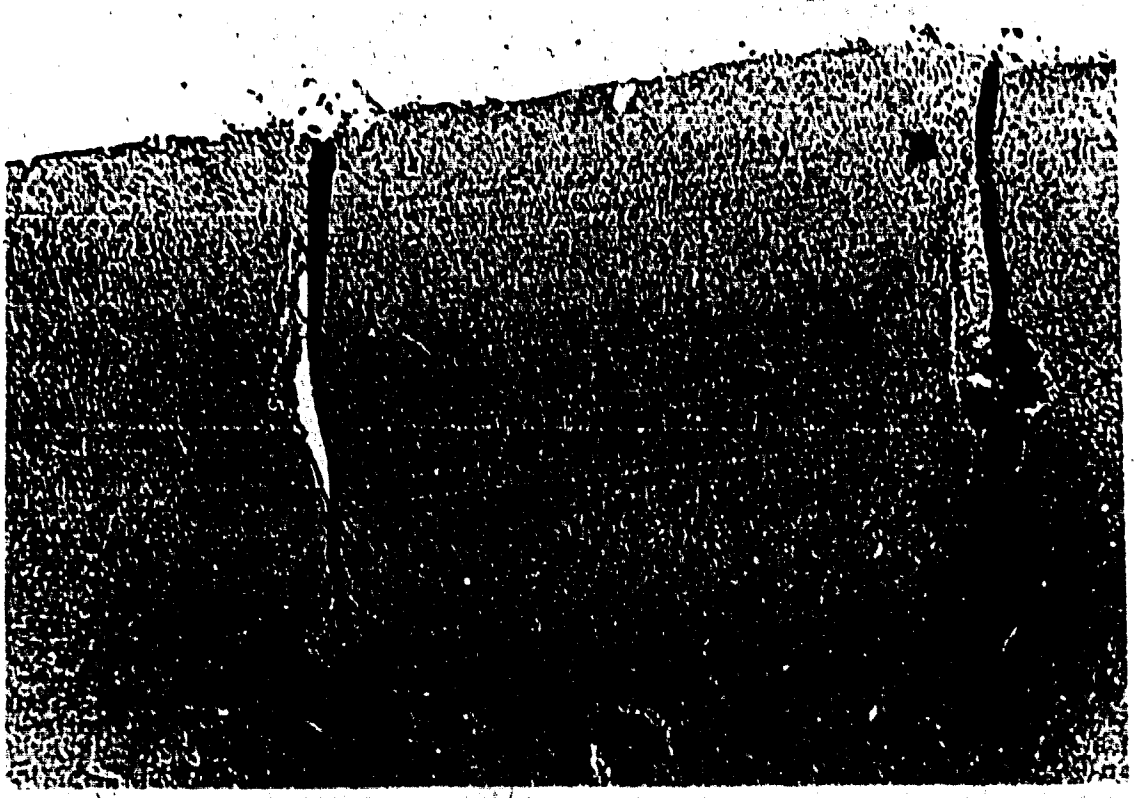


Plate 5. Subpial incisions on Cat 285. Weil-Weigert method; 31 x.

Plate 6 shows a considerable bleeding reaction. Further illustrations of subpial incisions are given in Plates 7 and 8, and an example from the subdural group is presented in Plate 9. Note that partial undercutting could not always be avoided.

Finally, macro- and microscopical examination of the brain belonging to Cat 26 showed that the lesion was not situated in the usual location but far more in the sensory region. This could explain why there was no reversal of the paw preference in this cat. The destroyed area (Plate 10) had a diameter of $\pm$ 1.2 mm.

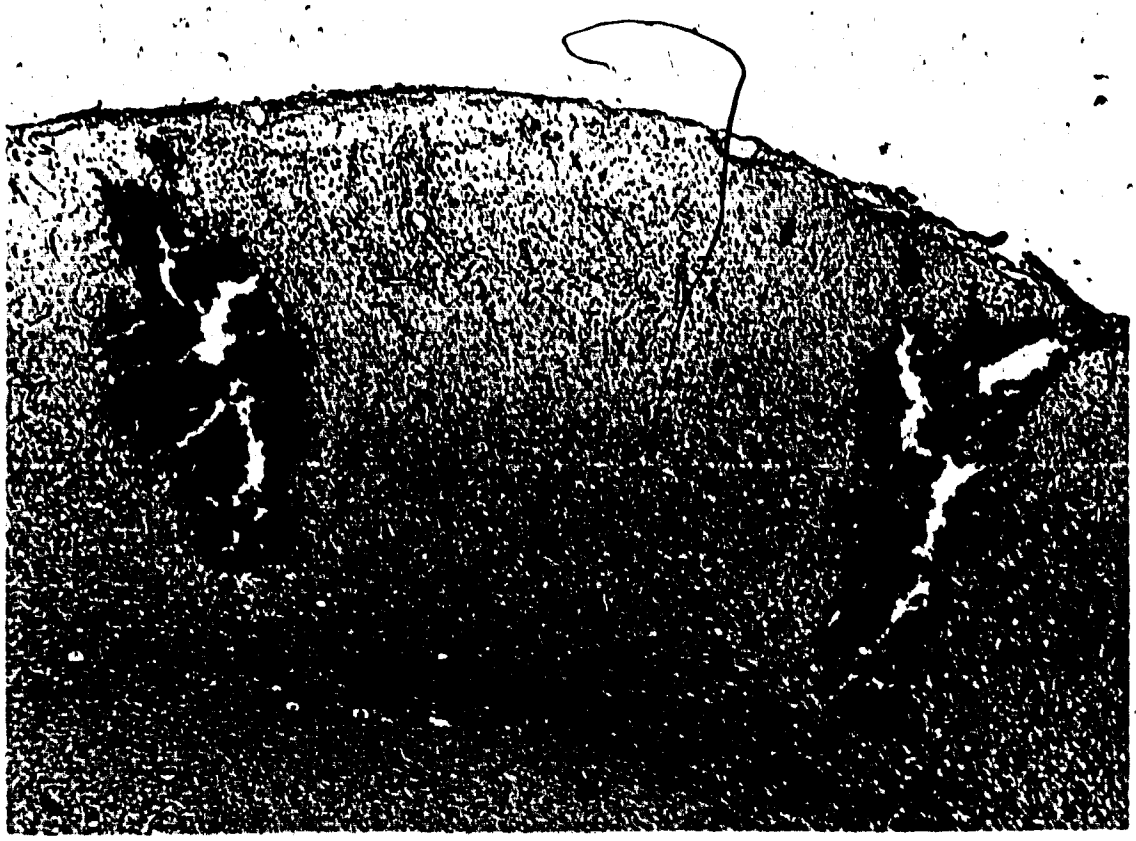


Plate 6. Subpial incisions on Cat 15. Weil-Weigert method; 31 x.

Plate 7. Subpial transections on Cat 59. Weil-Weigert method; 31 x.

Plate 8. Subpial transections on Cat 19. Weil-Weigert method; 31 x.

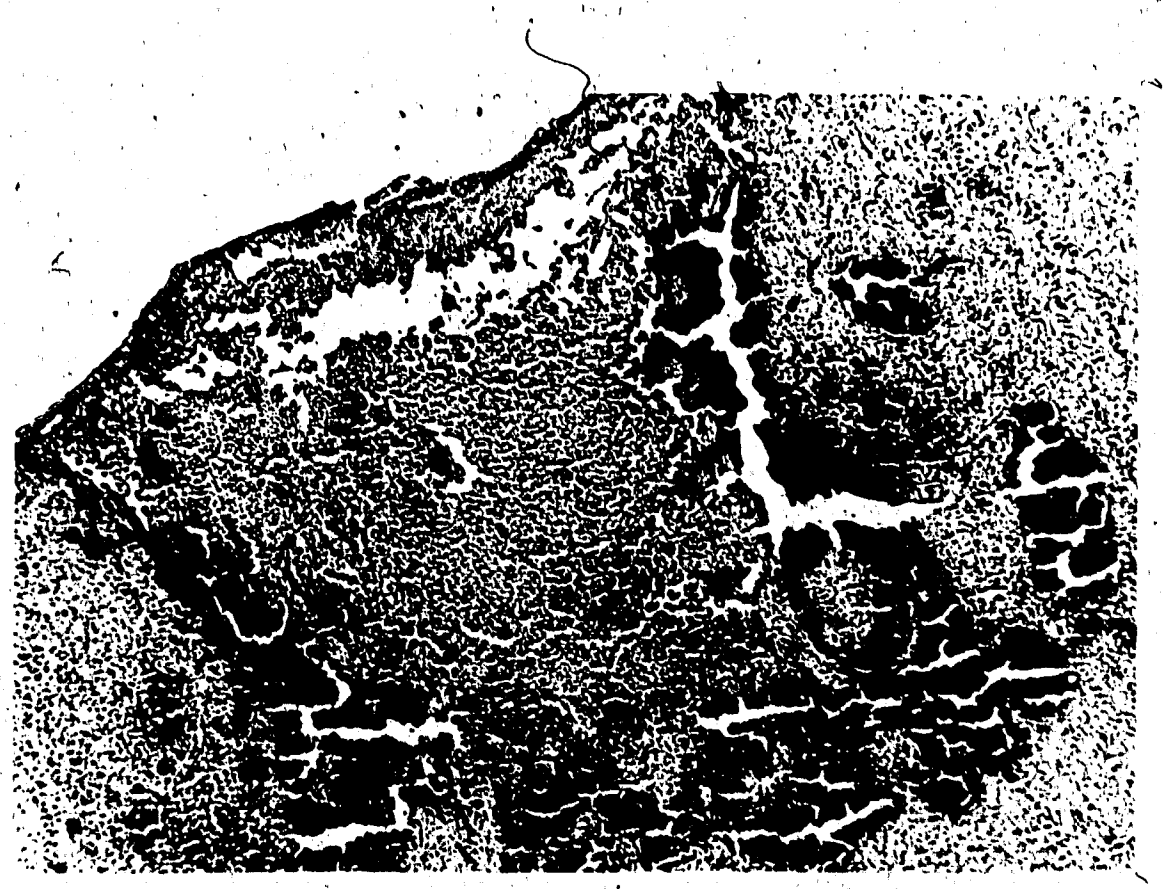


Plate 9. Subpial transections performed after subdural application of cobalt-gelatin on Cat 50. Weil-Weigert method; 31 x.

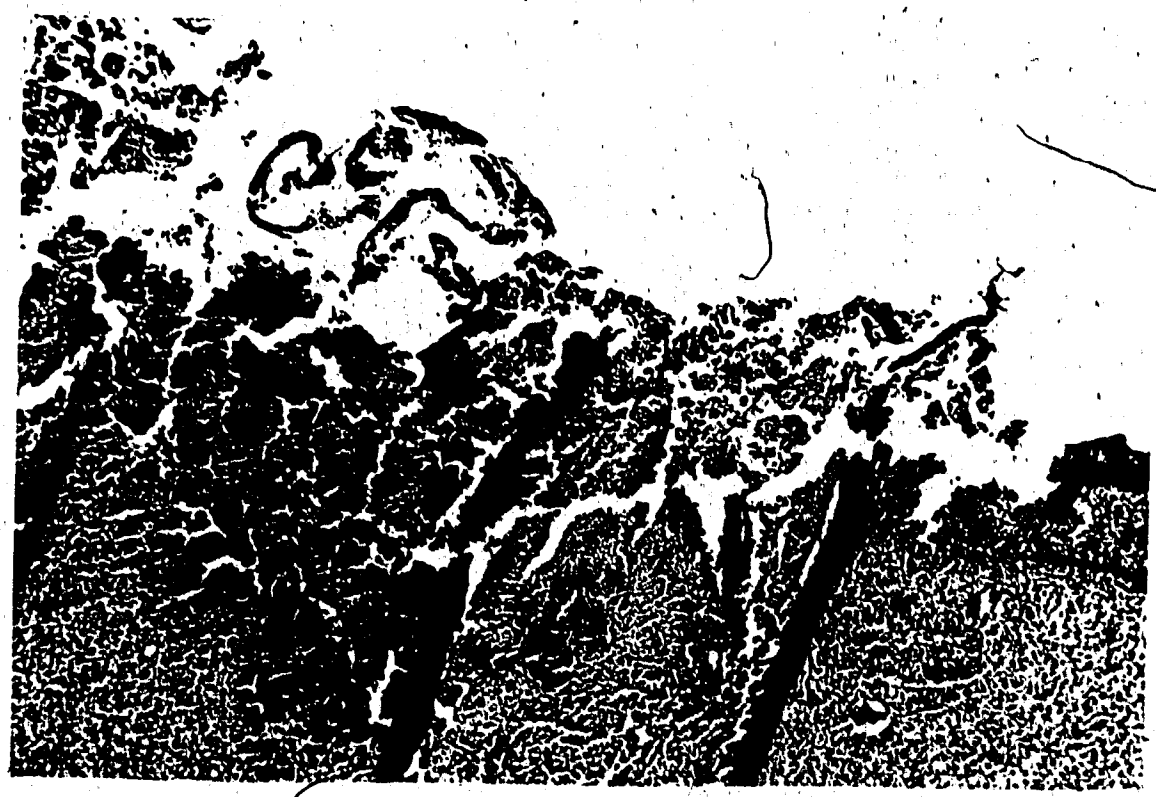


Plate 10. Topectomy on Cat 26. Weil-Weigert method; 31 x.

VII. DISCUSSION AND CONCLUSIONS

The results of these experiments throw some light on the original observations of Morrell and Hanbery (101) which showed that subpial vertical cortical incisions, forming squares of about 3 to 5 mm wide over an epileptic focus, are an effective surgical approach to the problem of focal epilepsy in humans.

Unlike subpial cortical undercutting, which results in an increased sensitivity to seizures of the isolated slab, this method of Morrell produces decreased tendency for hypersynchronization in the isolated slab.

It is assumed that vertical subpial isolation of the focus reduced the neuronal volume available for hypersynchronous activity. These experiments provide no direct information concerning the exact dimensions of the cortical mass involved in the EEG or EcoG spike generation. Nonetheless, it can be concluded that this mass must be at least 2 x 2 mm wide in the cobalt-gelatin focus of the cat.

It could be argued that the suppression of the spike focus is due to the scar formation. However, this is quite unlikely since pial scars are a well-known cause of epileptic activity in humans. Moreover, a simple coagulation of the focus (2 x 2 mm) was not able to stop spike generation (Cat 26).

The data obtained in our series of cats fit quite well with previous observations made by Tharp (137). This investigator also isolated experimental foci by making four subpial vertical cuts. However, he used penicillin foci in acute experiments on rabbits and the isolated

block of cortex measured 2 x 5 mm. When the cuts were made completely to the ventricle, he found that the isolated cortical mass was very difficult to render epileptic. The penicillin pledget had to be reapplied several times before "spikes" could be generated. Even then the "spikes" were quite different: with a lower rate of firing, a complex morphology and a higher amplitude. Since the penicillin had to be reapplied so many times, it seems reasonable to assume that deeper structures became influenced by the epileptogenic agent. This could explain the different shape and frequency of the so-called "spikes".

Tharp (137) mentions also that in most animals it was possible to trigger spikes in the isolated focus when a second focus was created 4 to 5 mm posterior to the original lesion. Such seizures did not spread to the normal cortex surrounding the cuts. As seen in the Introduction, this effect is quite common in experiments using cortical slabs. Both Torres (139) and Morrell (99) explain the unilateral spread of epileptic activity from a larger neuronal volume into a smaller by the principle of volume conduction.

In the present experiments, volume conduction cannot be excluded either. As reported earlier, there was one cat (# 267) on which the cobalt-gelatin was applied 3 days after the subpial isolation. As a result, no isolated spikes were seen, but instead ipsilateral hemisphere discharges were recorded with some components at the focus. Such spikes at the focus could have been the result of volume conduction from neighbouring cortex, or they could have been a reflection of subcortical activity.

The same can be said about the high amplitude sleep spindles which were recorded at the isolated focus in several cases. Was this a reflection of activity in neighbouring cortex, or did the spindles arise from the isolated cortex, which was driven by thalamic discharges? No answer can be given to this question yet. On the other hand, an explanation purely based on the role of the thalamus fits well with recent experiments done by Grimm et al. (55). It was found that KCl depression of the thalamus abolishes rhythmical phenomena, such as after-discharge burst, while spike events, originating in the cortex, remain.

An inverse situation is present in our investigation: subpial isolation of the focus abolishes the spike events, but activity with a thalamic origin is preserved. In fact, sleep spindles and hemispheric discharges were frequently observed at the focus while the focal spikes disappeared. Moreover, it is interesting to note that only once focal discharges were seen post-operatively (Cat 19) and that in this case a TRAIN of spikes was recorded which was also seen simultaneously at another electrode over the same hemisphere. This would indicate that the operation is able to stop hypersynchronization which has a cortical origin but is unable to affect discharges with a thalamic source.

Finally, from a clinical point of view, it is important to note that this surgical technique seemed to have some effect on the epileptic jerks as well (Cat 59 and Cat 84 which is not reported on in this thesis). However, one is well aware of the differences between human focal epilepsy and an experimental model with a

relatively short time course. It is only in these cases where the exact location of a purely cortical focus can be determined that some help can be expected from the application of the technique of Morrell and Hanbery (101). The superiority over previously used methods, such as topectomy, lies in the considerable reduction of the functional damage.

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