THE RELATION OF DEHYDRATION OF THE BRAIN TO THE SPREADING DEPRESSION OF LEAO

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PRELIMINARY CONSIDERATIONS

The spreading depression of Leão has been well established as a reproducible reaction in the lissencephalic rabbit (Leão 1944a b 1947 1945) The reaction can be initiated by weak mechanical or electrical stimulation applied to the surface of the pia-arachnoid membranes or it can also be initiated by intense neuronal activity It consists of a slowly expanding wave of depression of electrical activity moving through the cortex at a rate of 2 to 3 mm per min which persists at any point for from 2 to 6 min , and from which complete recovery sometimes requires 10-15 min It is accompanied by a striking variation of a D C potential After recovery the cortex exhibits approximately the same reactivity as it did previous to the depression wave

This Laboratory has corroborated many points in the above reports on 19 rabbits anesthetized with Dial However we found in 3 experiments on cats that the reaction was capricious in that animal (Marshall 1949) These experiments were done in December with the entire dorsal aspect of one hemisphere inadequately protected from room air Examination of specific sensory responses often showed evidence of irregular spread and decremental transmission of the reaction In contrast with the lissencephalic rabbit the irregularity of the reaction was striking in all of these experiments done on the convoluted cortex of the cat

There are impressive similarities between the suppressor reactions and spreading cortical depressions which are presented in detail by Sloan and Jasper (1950) There is some indication (Garol 1942 Gellhorn 1947 Marshall Woolsey and Bard 1937) that a common factor in these phenomena is the exposure of large areas of the cortex to room air

This consideration suggests that the pia-arachnoid mechanisms are crucially involved the low velocity of propagation the relatively long time during which the depression persists the vascular dilation which is reported to accompany it and other characteristics suggest a neurochemical reaction or a reaction complex involving at least one such step When the subarachnoid functions are impaired by exposure to room air normal chemical processes are altered and the reaction of Leão can take place

Accordingly two simple propositions were postulated for experimental tests The first is that the integrity of the pia-arachnoid system is more important than has heretofore been suspected If adequately protected from exposure to room air no spreading depressions should be observed following any kind of stimulation Secondly adequate internal dehydration of the brain should make it possible to secure regular, repeatable depression cycles in the convoluted cortex of the cat

METHOD

Cats were anesthetized with Dial or Nembutal, and rabbits with Dial to full surgical anesthesia, in some instances ether supplemented the barbiturates during operation if the latter anesthesia was slow in developing We have seen no differences between these

anesthetics as regards the depression reactions Likewise, depth of anesthesia is not critical Only large (4-5 kg) very healthy cats are recommended for this experiment A tracheal cannula was inserted and a mixture of 98 per cent O_2 and 2 per cent CO_2 administered when deemed necessary Exposure of the entire dorsal aspect of one hemisphere was made, the exposure usually extending across the midline about 1 mm The edges of the bone were covered with thrombin solution and if any marked increases of blood pressure were anticipated, the edges were lined with pledgets of gelfoam on which thrombin solution was again applied Because the exposure is later covered with oil hemostasis is a problem The dura was then carefully cut in strips, segments into which arachnoid veins or arteries entered were minimally disturbed, and the other segments were carefully folded aside As areas of pia-arachnoid membrane were exposed they were covered with pieces of Ringer's soaked cellophane. A wall of dental plaster (essentially $CaSO_4$) was then built up around the exposure. This was anchored on bone, strips of adhesive tape having been previously placed over exposed muscle and fascia to keep the wet plaster from extensive contact with tissues which might absorb some of the chemicals in the plaster We have seen no evidence that such absorption occurs to any significant extent, however The wall surrounding the exposure was built up to several mm above the highest point of exposed cortex Then the cellophane was removed from the pia-arachnoid and mineral oil at 37°C was poured in, to a minimal depth of 2-4 mm The dura can also be cut under the oil, providing more protection for the pia-arachnoid system Tests with 3 thermocouples placed very near the surface of the cortex in one experiment indicated a temperature of 35°C and that a temperature of 37°C could easily be maintained by external heating This series was done without application of heat to the oil pool on the brain

The recording electrodes usually used in this series of experiments were monopolars consisting of Ringer's soaked no 60 cotton threads in silver tubes The remote electrode consisted of a silver hook which was buried in fascia at some point on the calvarium outside of the plaster wall One electrode was placed on a somatic sensory area, usually Somatic I, and another on a visual area, usually Visual I Appropriate stimulation (tactile and visual) was applied as brief physiological stimuli in synchrony with the cathode ray oscilloscope traces (2 channels) at intervals of 2 to 4 sec The amplifiers driving the cathode rays were of 5 stages each, containing only one reactive coupling which was placed between the preamplifier and 4 direct coupled stages. Time constants of 0 05, 0 25, 0 4 and 2 5 sec were available on a panel switch The frequency characteristic was flat to 20 kc and down ½ at 50 kc The input grid current to the preamplifier stages was 10^{-9} amperes or less The input grid resistor was 3 3 megohms and, except for occasional checks, no input capacitive coupling was employed The overall common mode rejection was high (10,000-1) The recording sensitivity usually emp'oyed for the 5-inch cathode ray tubes was 10 μV per mm

Degeneratively balanced amplifiers were arranged to drive zero center meters for estimating the slow D C variations These were directly coupled to the preamplifiers, and in two experiments they were operated in parallel with the other recorders to obtain an estimate of the D C variations (Leão 1947) in the dehydrated brain experiments

A 2-channel paper recorder usually set at 25 μV /mm was operated in parallel with the cathode rays It was connected to the cathode ray driver stages through a capacitive coupling to the driver stages of the recorder

The method of stimulation was rather elaborate and served to eliminate uncertainties on this point The pulses used were rectangular waves (Marshall 1935, Offner 1946,

Rushton 1949) The circuitry employed for the pulse generators provided independent control of all parameters In this unit the output tube was a 6 L 6 triode connected, and operated as a cathode follower normally biased to below cutoff The cathode resistor was a 500 ohm linear potentiometer. The circuit was so designed that voltage output could be conveniently checked on an ordinary voltmeter and the equivalent output impedance was very low Arrangements were made to plot the current graph of each stimulating pulse on one of the D C amplifier-cathode ray oscilloscope channels

The stimulation technique must be very reliable when investigating capricious reactions, particularly so when absence of a slowly developing response is the crucial observation Completely non-polarizable electrodes, which can carry currents of 0 5 to 5.0 mA , are impractically cumbersome. The electrodes settled upon for these experiments consisted of no. 20 silver wires filed flat on the ends, held in a firmly mounted, adjustable holder and placed with flat ends flush on the surface of the pia-arachnoid to insure uniform current density

The rectangular stimulating pulses were made symetrically reversible by the output scheme shown in figure 1. This prevented long time erratic variations in stimulating current due to electrode polarization Constant current devices (Rushton 1949, Woodbury, Nickerson and Woodbury 1949) might serve this purpose also The electrodes were spaced 1 5 to 2.5 mm between centers Voltages used varied from 1 to 30 volts (D C peak) with currents of 0 4 mA upwards Standard test values usually used were 1 5 or 3 volts (D. C. peak) with currents of 0 4 to 1 6 mA at 50 cycles per sec applied for 5 sec

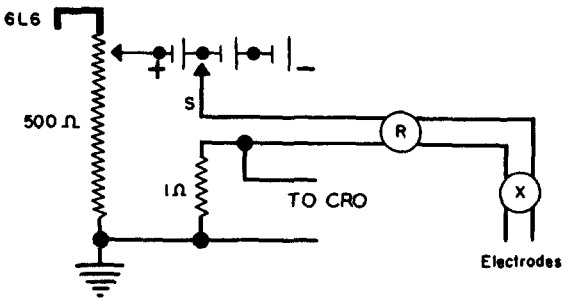

Fig 1

Output for depression initiating stimulator R is reversing switch, X is on-off switch used for starting and stopping stimulus train In these experiments, X was hand operated and duration of stimulus timed by watch, and rechecked by measurements on the low frequency paper record

RESULTS

Some of the data taken from the room air exposed brains of cats and rabbits in the midwinter period supplement the data reported by previous investigators who used only low frequency recorders Figures 2 and 3 illustrate the striate cortex complex of rabbit and cat in response to a single shock to the optic nerve The rabbit data is more accurate and definitive because of the above

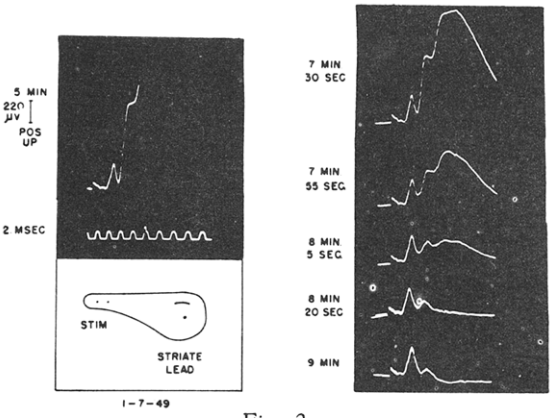

Fig. 2

Rabbit, Dial anesthesia 0 7 cc per kilo followed at 1 5 hrs by 0 2 cc per kilo additional Dorsal hemisphere of cortex exposed to room air Series of records showing effect of spreading depression on striate complex evoked by single shock to contralateral optic nerve Shock repeated cyclically at 1 per sec Bipolar depression initiating stimulus applied to anterior pole as indicated For this observation the stimulus was volts D C peak, 50 c/sec applied for 7 sec Times to left of records indicate time elapsed from start of depression stimulus The 5-min record represents control record taken before depression wave had invaded region of "monopolar" lead on striate cortex Gain of amplifier is high so that only start of a full size striate complex is on face of cathode ray tube giving a better view of the rabbit's relatively small radiation spike Positive is upward deflection

mentioned greater reliability of such preparations The pictures show the typical observation that the first spike (radiation spike) does not decrease during the spreading depression and that the events subsequent to radiation activity are almost completely eliminated in a reaction which is sufficiently profound to be termed a complete depression or suppression This conclusion was checked by recording the reaction in the geniculate and radiations with both bipolar and monopolar electrodes

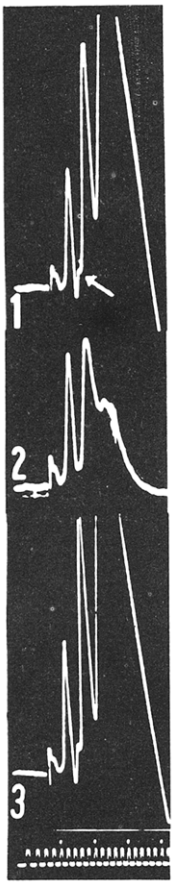

Fig 3

Cat, 1 6-49 Dial 0 65 cc per kilo Similar experiment to that of rabbit (fig 2), dorsal surface of hemisphere exposed to room air Depression initiating stimulus applied to anterior bend of suprasylvian gyrus, 4 5 volt D C peak 50 cycles, applied 5 sec Record 1 control prior to depression stimulus record 2 1 min after depression stimulus showing a partial depression record 3 at 8 min showing recovery The second spike mentioned in text indicated by arrow

The cat striate reaction (fig 3) show the same relation All events subsequent to the radiation spike are definitely decreased, including the small second spike indicated by arrow in figure 3

A point not emphasized by previous reports on these phenomena is the variability of the reaction Even in the rabbit experiments conducted with the brain exposed to room air show sufficient variability to produce both positive and negative errors unless a great number of observations are done The reaction may miss an occasional cycle or a spontaneous cycle of depression may occur and the sensitivity to mechanical stimulation may be very high so that a small unnoticed displacement of an electrode may initiate a depression cycle There is also a definite recovery time under certain conditions which will be more systematically discussed in another paper This recovery time may vary over a wide range from 6 min to 1 hour during the course of a long experiment Another point not emphasized in previous reports is the variability of the intensity of the depression reaction It can vary from a barely discernible partial to the profound degree shown in figure 2 The decline in specific sensory response parallels as a rule the decline of the spontaneous activity and the specific response is a more reliable index of the reaction

Three control experiments on cats were done with no dehydration These were set up with pia-arachnoid under the oil and test times were 4 3 5 and 9 hours respectively where test time is counted from time preparation is completed to termination of experiment No spreading depressions were seen in these experiments

Additional controls are to be found in the pre-dehydration periods of the 20 dehydration experiments These periods varied from 80 min to 6 hours and in only one case was a depression seen This brain one of the early oil pool experiments had been accidentally injured and one depression cycle subsequent to mechanical stimulation was seen Typical after-discharge and extinction phases were seen to follow the application of the 5 sec test stimulus (50 c /sec 1 5 to 9 V D C peak average current values varied from 0 5 to 5 0 mA)

Preliminary work with dehydrating agents injected through a branch of the femoral vein showed that 30 per cent saline 60 per

cent sorbital 75 per cent glucose and 50 per cent sucrose were ineffective All caused a little shrinkage but no significant removal of cerebrospinal fluid from the subarachnoid space (Bullock, Gregerson and Kinney 1935 Elliott and Jasper 1949 Weed and McKibben 1919) Ninety per cent sucrose, however when administered at 1 to 2 5 cc /min to a total volume of 12 to 30 cc per kilo resulted in very dramatic reduction in brain volume amounting to the order of 30 per cent However the experiment was very difficult The great rise in systemic blood pressure made hemostasis (particularly under the oil) a serious problem Pulse pressure was so high that the brain quite visibly pulsated and large artifacts appeared in the records during this part of the dehydration phase Diuresis was prolific and ascites commonly occurred

Of the 20 cat experiments in which 90 per cent sucrose was used 8 died in shock before the necessary degree of dehydration was attained In some of these death was hastened by hemorrhage from the incisions Lung pathology was a great hazard, as these cases would develop a serious trachea exudate or frank hemorrhage The general systemic strain was too great for a practical experiment in the sense of using the dehydrated preparation as a tool for further investigation of the mechanism Since the result was positive however a sufficient number of experiments was done to prove the point The successfully completed dehydrations numbered 12 Of these, 11 showed definite and typical spreading depressions which could be regularly elicited by the standard electrical stimulations as described above or by weak mechanical stimulation Spontaneous depressions were occasionally observed and in one case definite rhythmic spontaneous cycles were observed for over an hour In no case was it possible to elicit the spreading depression of Leão until the brain had shrunk 2 to 3 mm away from the lateral internal surface of the skull At this time cerebrospinal fluid was no longer visible under the arachnoid membrane The depression cycles under these conditions were regularly elicitable and not capricious and progressed through the entire dorsal aspect of the hemisphere Although these were the only areas examined there is little doubt that the reaction involved the entire hemisphere Measurements of the D C potential variations in 2 dehydration experiments confirmed the general relation reported by Leão (1947)

Many periods of abnormal types of electrical activity were seen to be associated with the depressions, but the discussion of that aspect is omitted in this paper

The dehydrated brains were generally only slightly less reactive as regards both spindles and specific sensory responses In some cases the reactivity was even enhanced This is an important condition if the dehydration experiment is to be considered valid The appearance of depression responses did not appear to depend on any decrease or alteration of general or specific neuronal activity

A curious feature of the dehydration process was the regular marked enhancement of both spindles and specific sensory responses during the early stages of dehydration after the brain had begun to visibly contract As the contraction proceeded to near the final stage the reactivity decreased to the region of normal for barbiturate anesthesia (fig 4) Development of shock did of course, promptly reduce brain reactivity and was usually first detected on the oscilloscopes

We attempted to rehydrate six of the dehydrated preparations with distilled water or hypotonic saline This superimposed another systemic stress and only one such experiment was successfully carried to completion In this case 200 cc of water were infused over a period of 92 min by which time the brain had expanded to approximately the pre-dehydration volume, cerebrospinal fluid was again becoming visible under the arachnoid, and the preparation no longer produced a depression for each test stimulus The preparation remained in the capricious

stage for 81 min , then during the succeeding 108 min it was impossible to elicit spreading depressions by any kind of electrical or mechanical stimulation The experiment was terminated while the preparation was still operating in good condition

Another of the six rehydration attempts was partially successful This was the preparation which we observed to be spontaneously and rhythmically producing depression cycles after completion of dehydration The period was first observed to be 6 min During the succeeding 101 min the period gradually lengthened to 12 min , then the definitely rhythmic character vanished, but spontaneous cycles of depression continued to appear sporadically for 109 min In the early part of the latter interval 0 6 per cent NaCl infusion was initiated and continued for 116 min at which time the preparation passed into shock During this interval the spontaneous cycles disappeared and systematic testing with electric shocks at 15 to 20 min intervals was resumed These repeated at first, then cycles began to be missed before shock set in The other four rehydration attempts were terminated by shock before significant reconstitution of the brain volume had occurred

The one failure of the 12 is the experiment in which we removed electrodes and devoted 0 5 hr to taking a picture of the dehydrated brain In the succeeding half hour no certain depressions were recorded at which time the animal passed into shock, but it is quite possible that spontaneous depressions were occurring during this interval It is very difficult to set up an experiment with electrodes properly placed for recording sensory potentials if the reactions are continually changing as a result of recurring cycles of depression

The following histopathologic report by Dr Benjamin Highman was made for the brain of the animal which was successfully rehydrated the specimen of brain tissue shows in many areas a slight to moderate, frequently perivascular infiltration of the meninges by neutrophils and fewed lymphoid cells A few neutrophils are seen occasionally in the subjacent gray matter Some of the smaller vessels in the brain appear partially collapsed and the Virchow-Robin spaces are often slightly widened In some vessels numerous neutrophils are seen in the lumen along the endothelium No definite changes are seen in the brain parenchyma

During the course of 28 experiments in

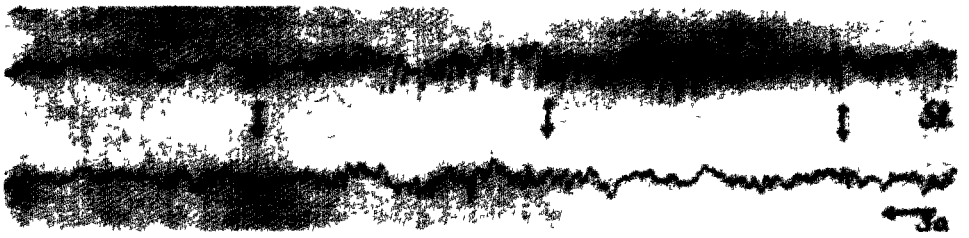

Fig 4

Dehydrated cat, wgt 4 4 kilo, 3-4-49, Dial 0 7 cc per kilo Intravenous 90 per cent sucrose, 16 cc per kilo within 70 min Record 86 min after start of sucrose injection, and 3 min 27 sec after depression initiating stimulus Latter applied at anterior bend of suprasylvian 3 volts D C peak, current of 0 7 mA 50 cycles for 5 sec Upper record, striate not yet invaded by spreading depression, showing the predominantly negative spindles seen in typical cat preparation under barbiturates when recorded with a "monopolar" electrode Reaction complex to brief photic stimulus to contralateral eye indicated by arrows Photic stimulus repeated at 3 5 sec intervals Lower line is somatic I in depression phase recorded by 'monopolar' electrode Spindles are absent and response to tactile stimulus applied to contralateral forefoot, at times indicated by arrows above, is negligible Time reads from right to left and positive is upward deflection

cats, both normal and dehydrated, many tests were made of various areas to determine if any of the so-called suppressor areas could be located as has been reported (Garol 1942, Gellhorn 1947) No such regional differences could be found If the preparation, either room air exposed or internally dehydrated, was regularly producing typical depressions, the depression could be initiated from any region on the dorsal aspect of the cortex

We also observed, in two rabbits, that the reaction could be initiated at a point remote from the stimulation site, presumably, by activation of association fibers This parallels the observation of Leão and Morison (1945) that the depression may be initiated in the opposite hemisphere by activation of commissurals This was clear in these two cases because the preparations operated in a stage of susceptibility to the reaction such that the reaction was not propagated from anterior to posterior along the cortical surface But the association fibers initiated the response posteriorly in the striate, and once well developed in that region, the reaction acquired a sufficient factor of safety in transmission characteristics to propagate forward and involve the somatic area There were other instances in which the reaction would thus skip cortical surfaces and develop with correspondingly shorter latencies in one or more other regions In the two experiments cited the reactions repeated the above pattern for several cycles with no significant variation, permitting definite observation

DISCUSSION

These experiments provide further confirmation of the work of Leão (1944a, b, 1947) and Leão and Morison (1945) which indicated that the spreading depression is a cortical phenomenon The depression of neuron function may be entirely secondary to some aberrant reaction of the pia-arachnoid system [1] The effectiveness of such diverse kinds of stimulation as electric shocks, mechanical deformation, or intense neuronal activity, suggests that each operates through some common mechanism These diverse means of initiating the reaction make possible many bizarre combinations of the reaction in experiments conducted with large areas of the pia-arachnoid exposed to room air The many points of similarity between these reactions and the available reports on the reactions with which the suppressor areas were mapped suggest that the latter reactions are spreading depressions Certainly many of the discussions (Dusser de Barenne and McCulloch 1941, Garol 1942) of the suppressor reactions contain descriptions of a creeping paralysis of activity similar to the spreading depression of Leão, and the experimental conditions were the necessary and sufficient conditions which permit capricious spreading depressions in convoluted brains The problems concerning specific inhibitory areas, functional inhibitory reactions, and specific suppressor areas (if any) are in a state of great confusion which has been clearly pointed out in a recent review by Clark (1949) These uncertainties do not apply to the various experiments dealing with the bulbar reticular region of Magoun (1944, 1946, McCulloch, Graf and Magoun 1946, Moruzzi and Magoun 1949) or the anterior limbic region of the cortex (Sloan and Jasper 1950), which reactions are qualitatively different from the spreading depression of Leão It is probable that this intriguing but abnormal reaction has confused experiments on cortical excitability since the time of Fritsch and Hitzig

We do not claim that these dehydration experiments demonstrate the long sought physiological function of the subarachnoid mechanisms The relation seems to be definite that when dehydration has proceeded to the point at which the cerebrospinal fluid is no longer visible under the arachnoid membrane that it then becomes possible to elicit the spreading depression However the dehydration is so extreme that a simple and certain conclusion cannot be justified We must assume that salt shifts may occur

[1] The data shown in figures 2 and 3 clearly show that the depression of activity is not due to randomization of activity

and that capillary permeability may be altered However experiments with dogs on rapid diuretic dehydration with 50 per cent sucrose 20 cc per kilo administered at 2 to 3 cc /min indicate no intracellular shift of sodium as estimated for the total system (Painter Holmes and Gregersen 1948) In our experiments the dehydration was more severe We can only conclude that this unphysiological condition is one way of regularly producing this abnormal reaction in the convoluted cortex of the cat

However the dehydration experiments provide further support for the hypothesis that spreading depression is dependent on an aberrant chemical reaction because the specifically neuronal activity is not radically altered The only obviously significant change in function is in the susceptibility to spreading depression The dehydration experiments can be logically interpreted as producing a crucial alteration of the mechanisms involved in the hypothetical neurohumeral reaction This supports the suggestion that dehydration of the pia-arachnoid system resulting from exposure to room air is an important factor in spreading depression It also accounts for the observations that lissencephalic brains are more susceptible to spreading depression Observations on the temperature factor involved in room air exposures will be reported later

If in normal, oil covered cat brains there is any reaction comparable to the Leão reaction but much more rapid, it is masked by the after-discharge and extinction interval or coincident with that interval This does not apply to the rabbit, in which species the oil pool prevents spreading depression in only about 50 per cent of our experiments

There are many aspects of possible mechanisms of spreading depression which might be discussed Since these experiments were primarily concerned with the necessary physiological condition, or substratum, only brief mention will be made of these possibilities A progressive electronic reaction may be involved, or a progressive depolarization of contiguous neurons may occur (Gerard and Libet 1940 Libet and Gerard 1941) The reaction certainly appears to be one depending on mere contiguity (Gerard and Libet 1940 Libet and Gerard 1941 Sloan and Jasper 1950) of neurons regardless of organization The D C voltage change probably has some interacting relation to neuron activity (Gerard and Libet 1940 Libet and Gerard 1941) but to date our attempts to demonstrate depressive effects (or enhancement) by applied polarization have produced no significant effects

This reaction is very complex In the cooled monkey cortex (Marshall Essig and Dubroff 1949) we have identified four components on the basis of velocity differences and one of these components apparently jumps the central sulcus We have also seen what appears to be the same components following prolonged exposure to room air Without detailed and specific evidence we consider it unprofitable to venture a hasty judgment as to whether these reactions should be labelled as essentially electrical or essentially neurochemical The basic condition can be produced by three methods with a high degree of probability for each These are deterioration due to room air exposure radical internal dehydration and cooling the cortex (Marshall Essig and Dubroff 1949) Hence we favor at this time the view that a chemical abnormality probably constitutes the necessary condition for this phenomenon

SUMMARY

1 Spreading cortical depression does not involve the radiation endings of the lateral geniculate fibers in the striate cortex

2 The reaction cannot be elicited by electrical stimulation in the cortex of the cat if the exposed brain is covered with mineral oil to a depth of 2 to 4 mm

3 The reaction can be regularly elicited if the cat's brain is internally dehydrated by intravenous administration of 90 per cent sucrose

4 The dehydration experiments as well as other evidence suggest that impairment of pia-arachnoid function is a necessary condition for spreading cortical depression

5 Arguments are advanced in support of the hypothesis that spreading depression is dependent on an abnormal neurohumeral reaction

6 No evidence of specific "suppressor" areas was found in the cat

REFERENCES

BULLOCK L T GREGERSON M I and KINNEY R The use of hypertonic sucrose solution intravenously to reduce cerebrospinal fluid pressure without a secondary rise *Amer J Physiol* **1935** *112* 82-96

CLARK G Suppression and facilitation A review *The Quarterly of Chicago Medical School* **1949** *10* 14-26

DUSSER DE BARENNE J G and MCCULLOCH W S Suppression of motor response obtained from area 4 by stimulation of area 4s *J Neurophysiol* **1941** *4* 311-323

ELLIOTT K A C and JASPER H Measurement of experimentally produced brain swelling and shrinkage *Amer J Physiol* **1949** *157* 122-129

GAROL H W The motor cortex of the cat *J Neuropath exp Neurol* **1942**, *1* 139-145

GELLHORN E Effect of afferent impulses on cortical suppressor areas *J Neurophysiol* **1947**, *10* 125-132

GERARD R W and LIBET B The control of normal and convulsive brain potentials *Amer J Psychiat* **1940** *96* 1125-1153

LEAO A A P Spreading depression of activity in the cerebral cortex *J Neurophysiol* **1944**a *7* 359-390

LEAO A A P Pial circulation and spreading depression of activity in the cerebral cortex *J Neurophysiol* **1944**b, *7* 391-396

LEAO A A P Further observations on the spreading depression of activity in the cerebral cortex *J Neurophysiol* **1947** *10* 409-414

LEAO A A P and MORISON R S Propagation of spreading cortical depression *J Neurophysiol* **1945** *8* 33-45

LIBET B and GERARD R W Steady potential fields and neuron activity *J Neurophysiol* **1941** *4* 438-455

MAGOUN H W Bulbar inhibition of motor activity *Science* **1944** *100* 549-550

MAGOUN H W and RHINES R An inhibitory mechanism in the bulbar reticular formation *J Neurophysiol* **1946** *9* 165-171

MARSHALL, W H Observations on blood pressure responses to electrical stimulation of the central end of the vagus *Amer J Physiol* **1935** *113* 95

MARSHALL W H Suppressor action on primary sensory projection reactions *Proc Amer Physiol Soc* **1949** *8* 107

MARSHALL W H ESSIG C F and DUBROFF S J The relation of the pia-arachnoid system to certain abnormal phenomena of the cortex *Eastern Assoc E E G* Baltimore Oct **1949**

MARSHALL W H, WOOLSEY, C N and BARD P Cortical representation of tactile sensibility as indicated by cortical potentials *Science* **1937** *85* 388-390

MCCULLOCH W S GRAF C and MAGOUN H W A cortico bulbo-reticular pathway from area 4-S *J Neurophysiol* **1946** *9* 127-132

MORUZZI G and MAGOUN H W Influence of bulbo-reticular stimulation upon electrical activity of cerebral cortex *Proc Amer Physiol Soc* **1949**, *8* 113

OFFNER F Stimulation with minimum power *J Neurophysiol*, **1946**, *9* 387-390

PAINTER E E HOLMES, J H and GREGERSEN M I Exchange and distribution of fluid dehydration in the dog *Amer J Physiol* **1948**, *152* 66-76

RUSHTON W A H A servo-stimulator *Proc Journ Physiol*, **1949** *108* 1

SLOAN N and JASPER, H H The identity of spreading depression and suppression *EEG Clin Neurophysiol*, **1950**, *2* 59-78

WEED L H and MCKIBBEN P S Experimental alteration of brain bulk *Amer J Physiol* **1919** *48* 512-558

WOODBURY L A NICKERSON M and WOODBURY J W Pulsed stimulator aids medical research *Electronics* **1949** Aug 84-85

Reference MARSHALL W H The relation of dehydration of the brain to the spreading depression of Leão *EEG Clin Neurophysiol*, **1950** *2* 177-185