SPREADING DEPRESSION OF ACTIVITY IN THE CEREBRAL CORTEX*

ARISTIDES A. P. LEÃO
Department of Physiology, Harvard Medical School, Boston, Massachusetts

(Received for publication August 14, 1944)

THIS STUDY originated in an attempt to secure more data for the understanding of the cortical electrogram which occurs in "experimental epilepsy," and of the conditions in which it is brought forth by electrical stimulation. Early in the development of the study an interesting response, elicited by electrical stimulation, was noticed in the cortex of rabbits. The distinctive feature of this response was a marked, enduring reduction of the "spontaneous" electrical activity of the cortex. We have endeavored to define experimentally some of the characteristics of this response.

METHODS

Almost all of the experiments were performed on rabbits. Dial narcosis was used routinely. The drug (dial-urethane solution, Ciba) was administered by intraperitoneal injection, in doses varying from 0.55 to 0.75 cc. per kg. of body weight. Nembutal was used occasionally; and chloralose, or ether were employed in several experiments. A tracheal cannula was always inserted. The animals were laid prone, with the head supported by a Czermak holder, and one or both cerebral hemispheres were widely exposed. Seven major cortical regions, according to Rose (37) are represented in the dorsolateral part of the hemisphere, investigated in this study: praecentralis granularis, praecentralis agranularis, postcentralis, parietalis, temporalis, occipitalis, and retrosplenialis granularis. The lead-off and stimulating electrodes were applied to the surface of the pia-mater. They were, as a rule, fine chlorided silver wires, with a small bead at the tip. Electrodes of the Ag-$AgCl_2$-agar-Ringer type, with a cotton tuft, were also used occasionally for recording. Electrical stimulation of the cerebral cortex was obtained with the "tetanizing" current of a Harvard induction coil, or with single condenser discharges delivered through a key operated by hand. The interelectrodal distance, for stimulation, was about 1.5 mm. in all cases. Amplification of the bio-electrical phenomena of the cerebral cortex was obtained with a six-channel Grass ink-writing oscillograph. The input of each pair of electrodes was on push-pull. The animal was, as a rule, grounded through the tracheal cannula, but in the experiments in which single condenser discharges were applied to the cortex while electrograms were being taken, a "Wagner ground" was used, in order to control the stimulus artifact. The balancing circuit consisted of a 10,000 ohm potentiometer shunted across the stimulating electrodes and with the center tap grounded.

Several experiments were carried out on pigeons, under nembutal narcosis, and only a few on cats. In the latter, the brainstem was transected at the intercollicular level, while the animals were under ether. The observations were made later, after elimination of the anesthetic. This preparation has been described by Bremer (11), who designated it the "cerveau isolé." Nembutal was also used in cats.

RESULTS

Unless otherwise stated, the results described were obtained on rabbits under dial narcosis.

---

* From a thesis submitted October, 1943, in partial fulfillment of the requirements for the degree of Doctor of Philosophy, Harvard University. An abstract of this paper was published in *Fed. Proc.*, 1944, *3*: 28.

Different, regional patterns of the so-called "spontaneous" electrical activity of the cerebral cortex were clearly recognizable. These patterns resemble the "Feldeigenstromtypen" described by Kornmüller (30, 31).

Depression of Activity

A. Depression of "spontaneous" electrical activity of cerebral cortex, caused by electrical stimulation. Following a brief period of repetitive electrical stimulation of the cerebral cortex (1 to 5 sec. of "tentanizing" current from a Harvard induction coil), a response consisting of a marked, enduring depression of its "spontaneous" electrical activity was observed. This type of response was obtained when the stimulation was below threshold for the production of any electrical "after-discharge."

If the lead-off electrodes were placed in the close vicinity (1 to 2 mm.) of the stimulated region, a depression, in progress or already well established, could be seen immediately after the period of stimulation, or else it could be noticed only after an interval (10 to 20 sec.), during which the spontaneous electrical activity of the cortex did not show any alteration. This "latency" for the appearance of the depression depended on the strength and duration of stimulation. It was longer when the intensity of the shocks was weak or when the period of stimulation was brief. Figure 1 illustrates a typical response. The arrangement of the electrodes is shown in the inset. In A the spontaneous electrical activity is seen. In B, C, D, and E, a continuous record, starting less than 1 sec. after the stimulation, the progress of the depression is seen. During the time (about 1.5 min.) between E and F, the electrogram was similar to that in E. The gradual return to the original spontaneous activity is seen in F, G, H, I and J, which are representative steps of its long course. The duration of this depression was variable. The first signs of "recovery" were often observed earlier than in the response illustrated, or they might appear later, a marked depression then persisting for a few minutes. Usually, in light narcosis the first signs of recovery were noticed early, and the recovery was rapid. In those regions in which the pattern of the spontaneous electrical activity is characterized by recurring "bursts" of discharges (for instance, the area precentralis granularis, of Rose), these bursts typically constituted the first signs noticed in the slow recovery. The voltage of the successive bursts gradually increased, and the bursts became more frequent. As a rule the slower waves between the bursts did not appear until later. In the recovery of the area striata, groups of the characteristic, slow waves separated by periods without them were seen for several minutes before the original pattern was reconstituted.

As a rule, the depression was seen merely as a progressive diminution of the background of potential fluctuations, without any sign of specific patterns. Occasionally, however, the initial pattern became simplied, and a more regular rhythm predominated until the depression became complete (Fig. 2).

B. *Spread of depression.* Simultaneous records from several pairs of electrodes showed that the depression spread out slowly, in all directions, from

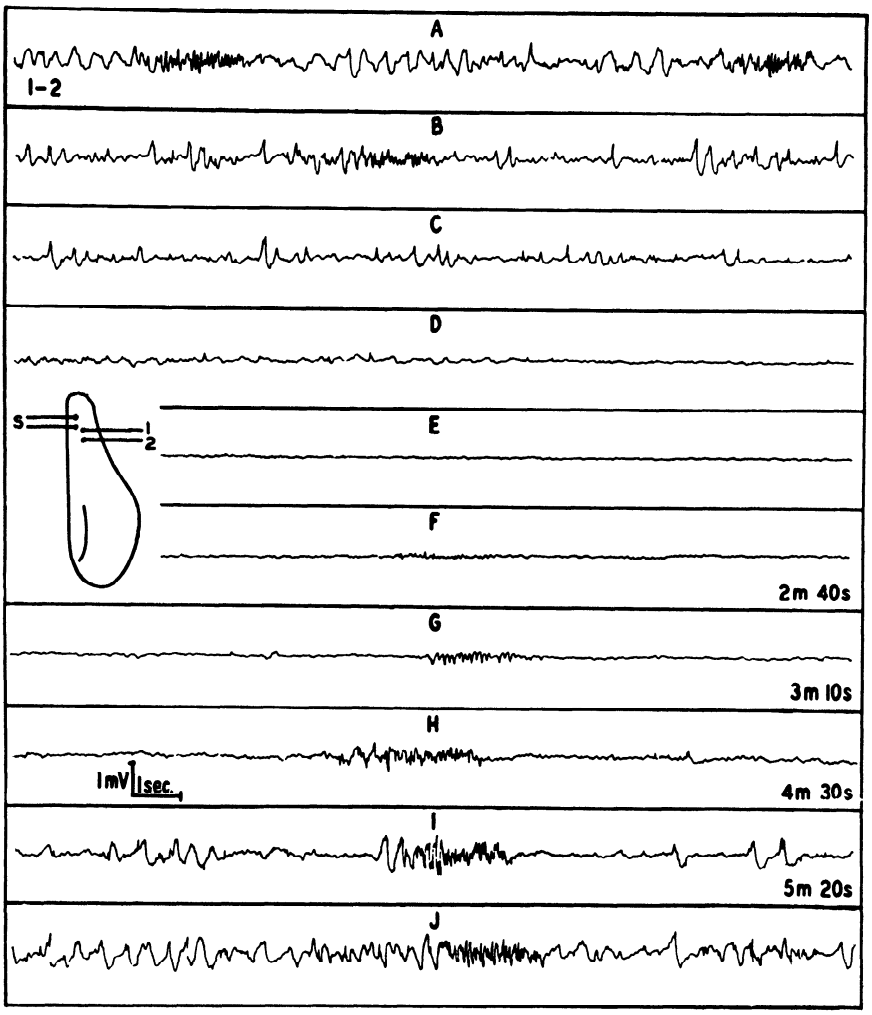

FIG. 1. Depression of the spontaneous electrical activity at the region stimulated. Stimulating (S) and recording (1–2) electrodes arranged as shown in the inset. A. Before stimulation. B to E. Continuous record starting less than 1 sec. after the end of stimulation. F to I. Records, corresponding to the times noted, after stimulation. J. Complete recovery, 5 min. after I.

the region stimulated, so that increasingly distant parts of the cortex were successively involved, *i.e*, they exhibited also a marked, enduring depression of their electrical activity. Figure 3 illustrates this spread. The time after stimulation at which each of the representative steps was taken, shows the slow rate of travel of the response. A response started near the frontal pole might take more than 5 minutes to reach a region near the occipital pole. From the stimulated region, the wave of depression spread out to almost all of the cortex exposed in the usual preparation. The only exception noted was

a small region, medial to the parasagittal sulcus. This region corresponds to the area retrosplenialis granularis dorsalis (Rsg β) of Rose (area 29d of Brodmann [12], area u of Droogleever Fortuyn [18]). The spontaneous electrical activity in this area did not show any appreciable decrease while the depression spread along adjacent regions (Fig. 4).

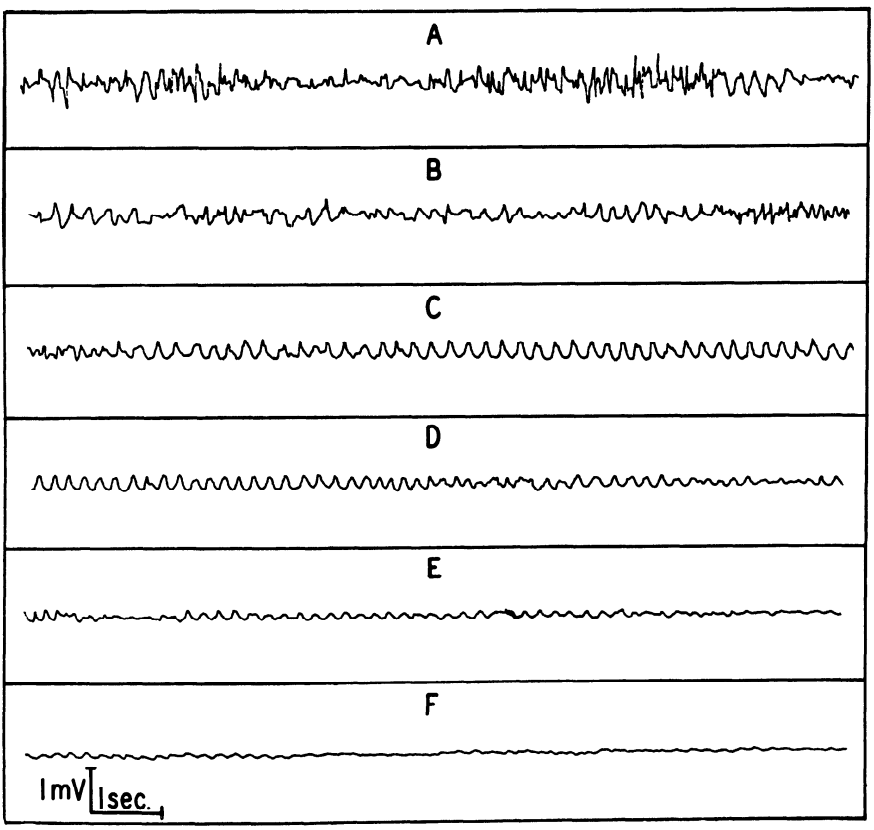

FIG. 2. Relatively unusual mode of onset of depression. Stimulus and record as in Fig. 1. A to F. Continuous record, starting immediately after stimulation.

At any one place on the cortex, not in the close vicinity of the stimulating electrodes, the depression of the spontaneous electrical activity developed gradually. About 20 seconds to 1 minute elapsed from the moment that the first signs of depression were noticed to the time when depression was maximal. During this time, as a rule, a mere progressive diminution of the background of potential fluctuations was seen. Occasionally, however, as in the region stimulated, a more regular rhythm predominated until the depression became complete. The electrical inactivity then persisted for a variable time, as in the region stimulated. Here again, the recovery showed a slow course, and usually it took several minutes for the electrical activity to return completely to normal.

When the recovery of the regions near the stimulating electrodes was rapid, the spontaneous electrical activity might have returned more or less to "normal" there, while the response was starting in distant parts (Fig. 5). The spread of the depression within a given cytoarchitectonic area was progressive, *i.e.*, the spontaneous electrical activity in these units did not change

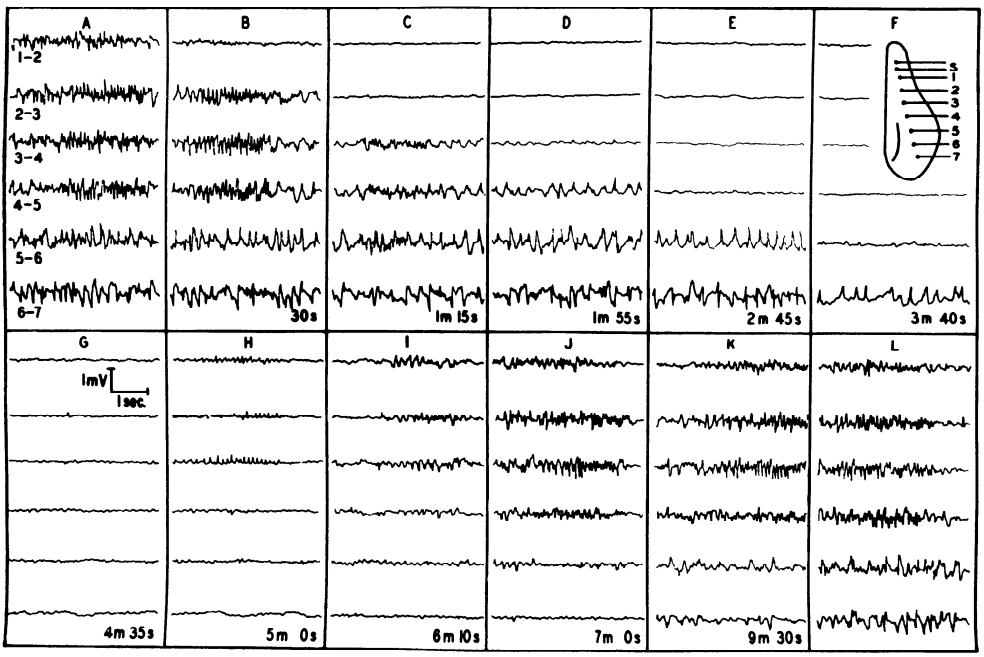

FIG. 3. Gradual spread of depression. Electrodes arranged as shown in the inset. A. Before stimulation. L. 7 min. after K.

In this and the following figures, when a strip is timed, that time indicates the interval from the end of the stimulation period. Upward excursions in the records denote negativity of the more frontal electrode (lower number) with respect to the more occipital electrode (higher number). Unless otherwise mentioned, the stimuli were induction shocks at "tetanizing" frequency, applied for 3 to 5 sec. through electrodes S.

simultaneously all over the area; one part might still be active while another portion was depressed. After a wave of depression had spread over the cortex, it took several minutes (5, 10, or even more) before the spontaneous electrical activity returned to normal in all regions. A second spreading response could be elicited earlier than this, but not until the recovery was well advanced at the region stimulated.

C. *Mechanical stimulation.* Spreading depression of the electrical activity could also be elicited by mechanical stimulation of the cerebral cortex. One or a few light touches with a small glass rod evoked it easily. These mechanical stimuli caused only a slight compression of the tissue, without any visible structural damage. The point touched could not be distinguished later from the neighboring cortex. Depression then appeared at the stimulated region

after a variable latency (10 to 40 sec.). It progressed and spread over the cortex, as described. When electrodes were being placed on the pial surface, responses were occasionally elicited by this mechanism.

D. *Regional differences.* Stimulation of the frontal regions of the hemi-

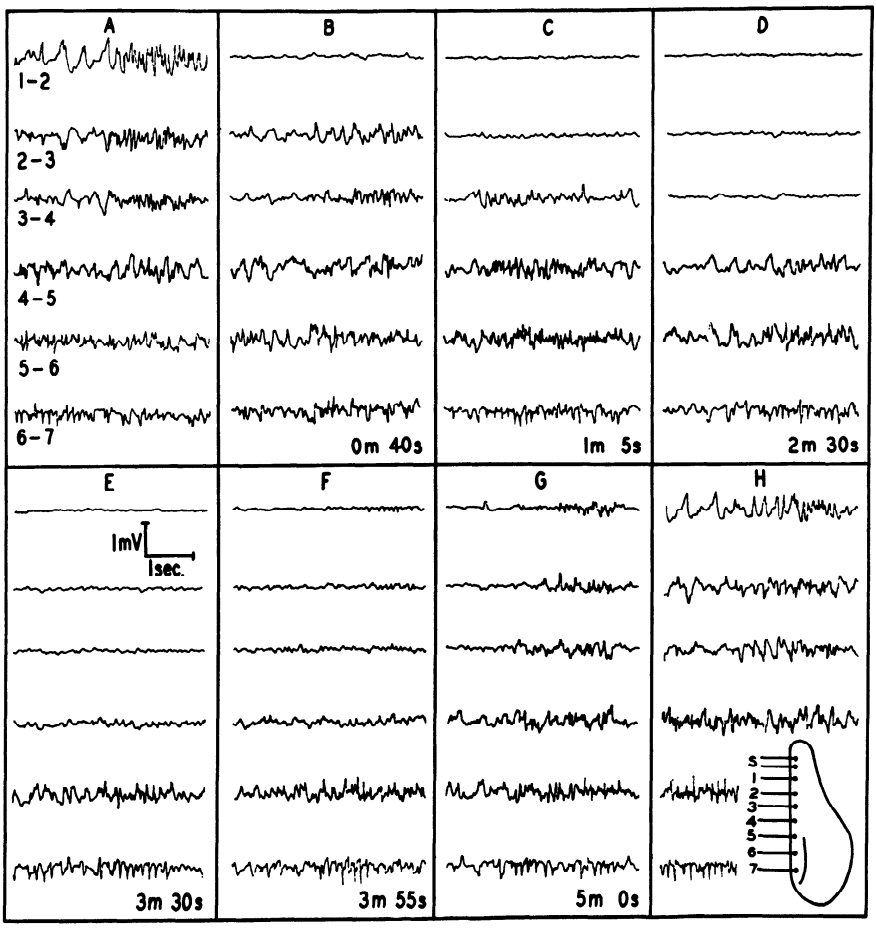

FIG. 4. Absence of spread of depression to the area retrosplenialis (electrodes 6 and 7, see inset). A. Before stimulation. H. Recovery, 6 min. after G (see legend of Fig. 3 for additional explanation).

sphere with appropriate weak intensity was followed invariably by a typical response. The wave of depression traveled throughout the exposed cortex, with the exception noted above. Responses were also easily obtained when the stimuli were applied to regions about midway from the frontal to the occipital pole. The depression would then spread out slowly in all directions, and would reach the regions near the two poles of the hemisphere at about the same time. The results of stimulation of regions near the occipital pole,

for instance the posterior part of the area striata, were more variable in different animals. A typical response would often be elicited with weak stimulation, but sometimes stronger stimuli were required than those effective in the frontal regions. In certain cases, a stimulation was required that was strong enough to produce a brief "after-discharge" in the close vicinity of

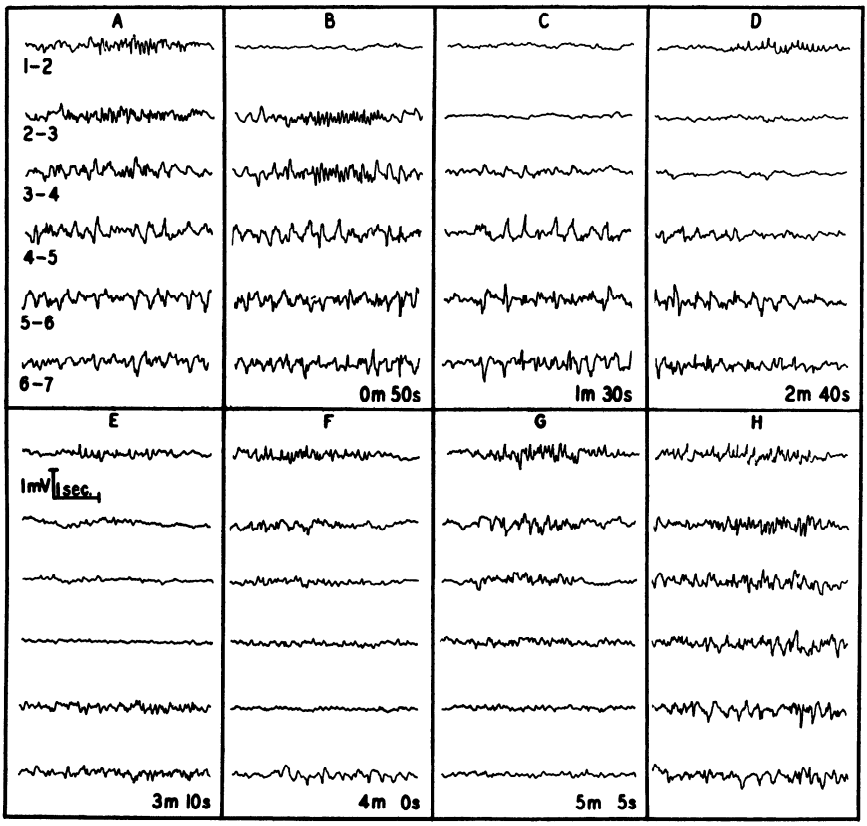

FIG. 5. Rapid recovery of spontaneous activity in regions near the stimulating electrodes. Electrodes arranged as in Fig. 3. A. Before stimulation. H. Complete recovery; record taken 3 min. after G.

the stimulating electrodes. This brief "after-discharge" was confined to this region, and was followed, usually after an interval of several seconds, by depression of the electrical activity which then spread out in all directions and ultimately reached the frontal pole. Finally, in a number of animals a widespread wave of depression could not be elicited at all by stimulation of the more posterior portions of the area striata. A brief depression of the electrical activity could be seen at the stimulated region, and sometimes it spread out for only a few millimeters. While it was sometimes difficult to initiate a spreading wave of depression from the area striata, it was always possible,

however, to involve this area in a response, *i.e.*, to have its electrical activity depressed, by stimulation of the more frontal regions of the hemisphere.

In regions of the cortex other than the area striata, if the strength of the stimulus was sufficient to produce a local brief "after-discharge," this activity was followed by depression which then spread out as described. Although the depression was marked all over the cortex, it was as a rule somewhat more conspicuous and enduring at the regions in the anterior half of the hemisphere, especially the more frontal ones.

If only minimal effective stimuli were used, which were well below threshold for the production of any electrical "after-discharge," the response at any one particular region of the cortex had the same time course and magnitude whether the stimuli were applied near or far, and regardless of the region stimulated. Two waves of depression could be started simultaneously at distant regions of the cortex. They then spread in the usual manner, so that two waves might travel in opposite directions to reach an intermediate cortical region.

E. *Mechanism of spread.* The spread of depression could be delayed or entirely prevented from reaching some part of the cortex by applying for a few minutes in appropriate positions on the pial surface strips of filter-paper soaked with a solution of cocaine hydrochloride (10 per cent). Damage to a narrow band of tissue by application of a hot wire, or a superficial cut, also interfered with the spread of the depression. This evidence suggests that the spread of the depression is a cortical process, *i.e.*, it takes place within the gray matter, or perhaps it also involves the underlying white, but it probably does not require a contribution from sub-cortical centers.

F. *Elicitation of depression in opposite hemisphere.* The depression of the electrical activity could also be elicited in the opposite hemisphere. In this case, the response appeared first at the region symmetrical to the one stimulated, and spread out from there to the rest of the hemisphere. If very weak stimulation was used to start a response, it usually did not cross. No change was then noticeable in the spontaneous electrical activity of the opposite hemisphere, throughout the time the depression was spreading in the stimulated side. If the strength of the stimulation was increased a little, the crossed response was obtained, but at the symmetrical region the "latency" for the establishment of the depression was longer than it was at the stimulated region, so that the spreads in the two hemispheres were not coincident. In the crossed side it started a little later, and, as a rule, at any given time after stimulation, it had covered a smaller area than that reached on the stimulated side. The crossing was much more easily obtained by stimulation of the anterior half of the hemisphere, especially the more frontal areas.

G. *Depression of sensory responses.* (1) *Responses in the somatic sensory cortex.*—The area in the rabbit's cortex, which receives the afferent impulses relayed from tactile and other receptors of the body and limbs has been mapped by Adrian (2). Cortical responses to mechanical stimulation of the somatic receptors—light taps on the forefoot, the hindfoot, or the lips, or

movements of the vibrissae—were easily recorded. In Fig. 6 I is illustrated a typical response to a light tap on the forefoot. The responses consisted of a brief potential wave, positive with respect to an electrode outside the responding area, always clearly recognizable, followed immediately in most in-

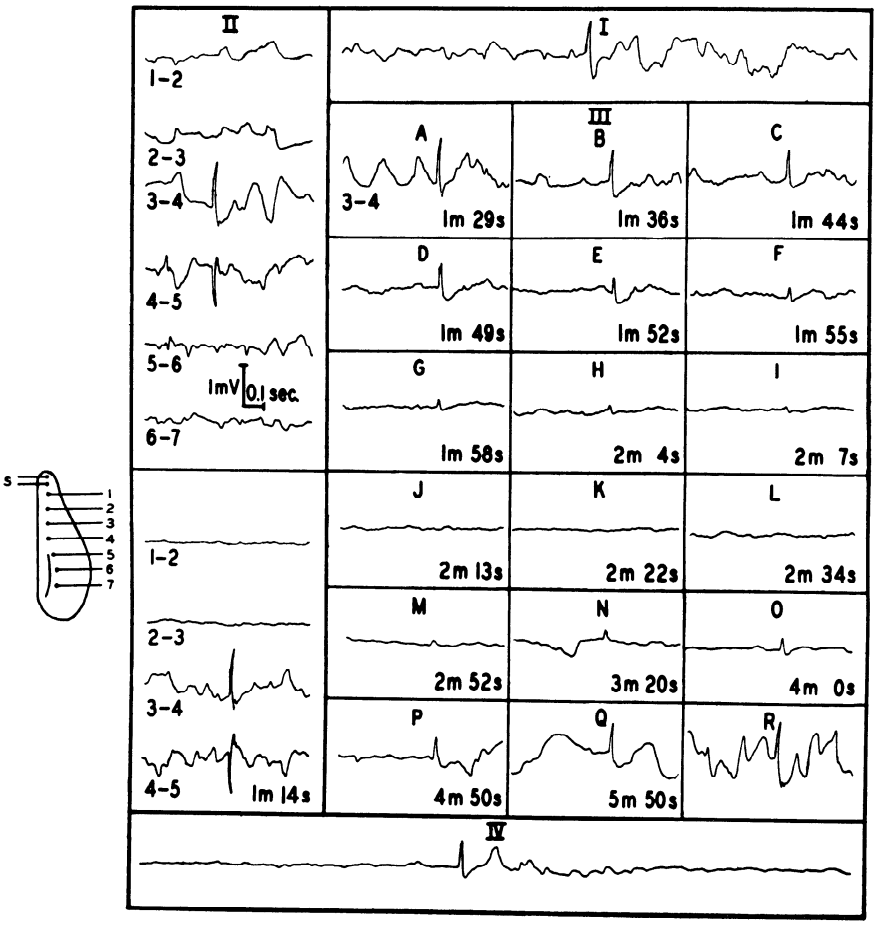

FIG. 6. Depression of responses to touch. Electrodes arranged as shown in the inset I. A typical response. II. Upper section: simultaneous records, showing the response localized to electrode 4. Lower section: record taken 1 min. 14 sec. after stimulation (the depression has reached electrode 3; the responses, at 4, are unimpaired). III. Continuation of II, showing the depression of the responses when the process reaches electrode 4 (R, complete recovery, was taken 8 min. after Q). IV. A response, during the recovery of depression, showing the complexity of the events elicited by each tactile stimulus.

stances by a negative excursion, more variable in amplitude and duration. There were also later components, variable, and difficult of description because of the interfering spontaneous excursions. If the stimulation was repeated about every 3 seconds, a series of quite similar responses was ob-

tained. While a series of tactile stimuli was thus delivered continuously, if a spreading depression was started at any distant region of the cortex, the following results were observed. The sensory responses, much as the spontaneous electrical activity, remained unchanged until the advancing front of the depression wave reached the region in question. Then, both the sensory responses and the spontaneous activity declined gradually and approximately in parallel. A few small sensory responses were usually obtained after the spontaneous excursions had ceased to be noticeable, but for a short time, at the peak of the depression, the responses could no longer be recognized. The sensory responses reappeared relatively early in the recovery period and increased gradually, over an interval of several minutes, to reach their initial amplitude at about the same time as the spontaneous activity. Figure 6, II and III, illustrates a typical observation with a number of representative steps. The responses, in the progress of the depression, might be reduced to single positive waves, but often a small negative phase followed even when the positive component was greatly reduced. Late in the recovery, while the spontaneous electrical activity was still considerably reduced, the complexity of the sensory responses was clearly manifest (Fig. 6 IV). If, early in the depression, the amplification of the electrogram was increased, a sensory response could still be recognized with ease, when it had become barely noticeable with the usual amplification. At the peak of the depression, however, no wave could be distinguished as a separate response from the small oscillations of the background.

Characteristic sensory responses could be elicited in one hemisphere throughout a depression of the opposite hemisphere. The responses to electrical stimulation of a spinal afferent nerve were also examined. The progress of the depression and the course of the recovery of these sensory responses, elicited by single shocks applied at intervals of about 3 seconds to the contralateral ulnar nerve, were similar to those described for the responses to mechanical stimulation of the receptors.

(2) *Optic responses.*—These responses have been described in detail by Bartley, Bishop and O'Leary (5–10). The responses of the area striata were evoked by illumination of the eye. The contralateral retina was illuminated for about 2 or 3 seconds, every 5 or 6 seconds, and "on" or "off" effects were observed, or else a brief flash of light was used, repeated at intervals of about 3 seconds. The depression and recovery of the optic responses occurred again in a manner similar to that described for the responses in the somatic sensory cortex. The electrograms decreased in amplitude but, as a rule, remained complex until they were well depressed. Figure 7 illustrates a typical observation. Owing to the large extent of the responding area, the progressive spread of the depression of the responses inside the area striata was easily observed. Three or 4 electrodes were placed on this area, in line along the direction of spread of a wave of depression started at some distant region. When the wave reached the first electrodes the responses were depressed there while still unaffected at the remaining ones. Subsequently the

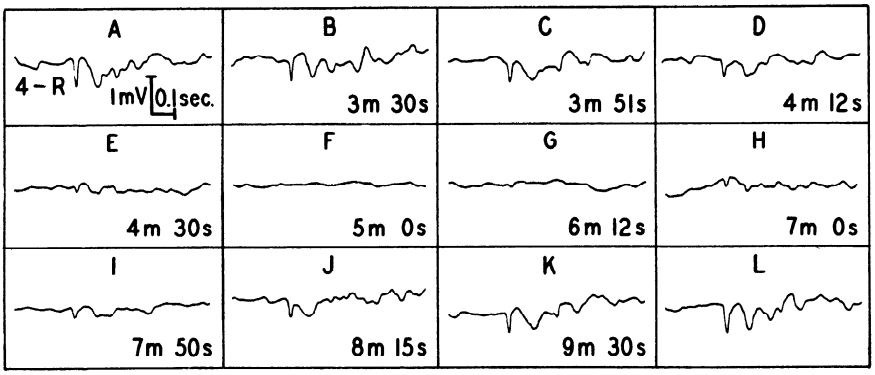

FIG. 7. Depression of optic responses. Electrodes arranged as in Fig. 3. R. Indicates a reference, extracortical electrode. A Typical response, before stimulation. L. Complete recovery, record taken 4 min. after K.

entire area was involved, and the gradual recovery of the responses occurred in the same sequence as the depression.

H. *Depression of responses to electrical stimulation of cortex.* (1) *Responses in the vicinity of a region stimulated with single shocks.*—A complex response starting with a distinct potential wave, during which the electrode proximal to the stimulated region went positive with respect to the distal one, was recorded with the electrodes arranged in the manner shown in the diagram accompanying Fig. 8. While a series of single shocks was being delivered, about one every three seconds, a spreading depression was started at a distant region. The depression and recovery of the responses, as the wave of depression passed through the recording region, are shown in Fig. 8, with representative steps taken at different times. The series has the same general features as those presented for the sensory responses.

(2) *Responses in contralateral hemisphere.*—These have been described by Curtis (15, 16). The responses were evoked by single shocks applied to the pial surface on one side, and were recorded from the opposite hemisphere at the region symmetrical to the one stimulated. They consisted of an initial

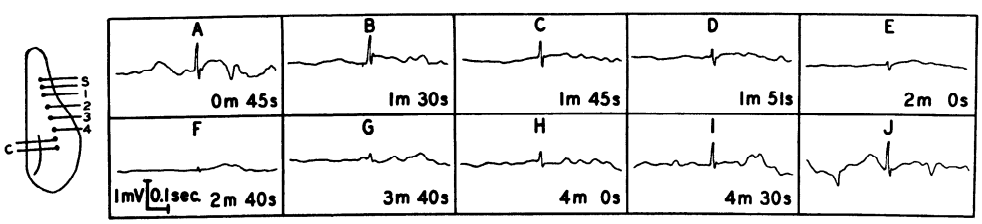

FIG. 8. Depression of the responses to electrical stimulation of the cortex. Responses recorded in the vicinity of a region stimulated with single shocks. Single shocks (condenser discharges) delivered through electrodes C. Responses recorded from electrodes 3 and 4. The response illustrated in A was similar to those before the stimulation eliciting depression. J. Complete recovery; record taken 8 min. after I.

potential wave, positive with respect to an electrode outside the responding area, always clearly recognizable, followed immediately in most instances by a negative wave, variable in amplitude and duration, and by other later components. With electrodes arranged as shown in the diagram (Fig. 9), a

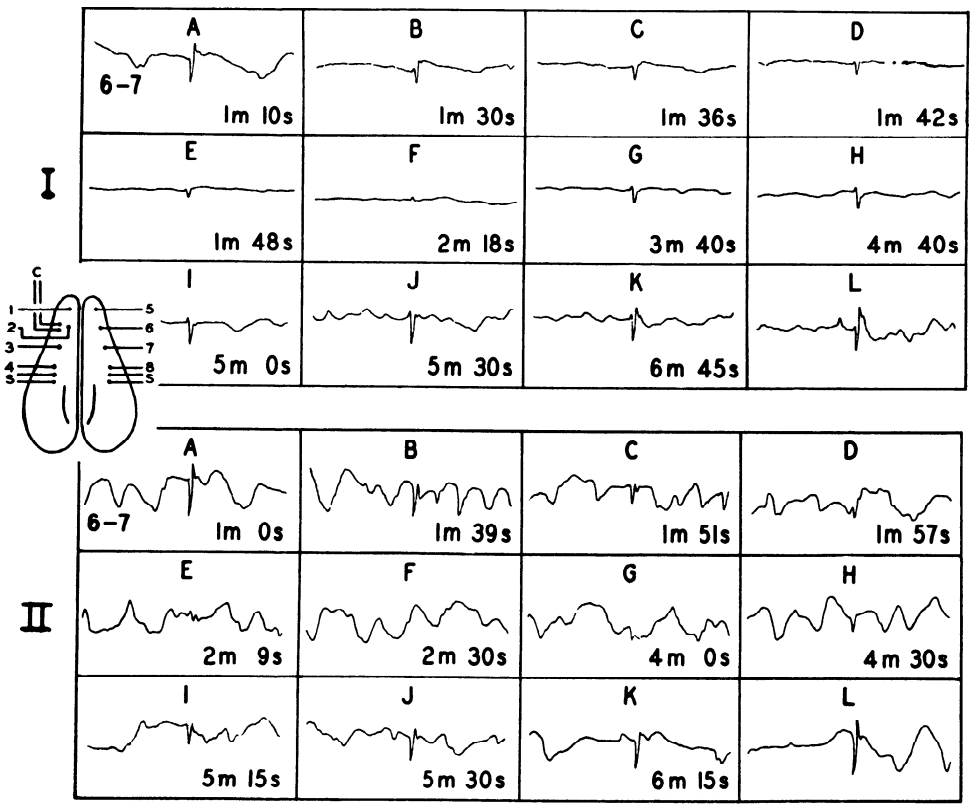

FIG. 9. Depression of the responses elicited in the contralateral hemisphere by single shocks applied to the pial surface. Single shocks (condenser discharges) applied to *left* cortex, through electrodes C. Responses recorded in the *right* hemisphere, from electrodes 6 and 7. I. Depression spreading over *right* hemisphere (elicited through electrodes S, right). The response in A is similar to those recorded before the stimulus was applied at S. L. Complete recovery, 7 min. after K. II. Depression spreading over *left* hemisphere (elicited through electrodes S, left). The response shown in A was similar to those before the stimulation eliciting depression. L. 5 min. after K.

spreading depression was started in either hemisphere, and its unilateral spread was ascertained. The single shocks were repeated about every 3 seconds, and a series of quite similar responses was obtained. While the single shocks were being delivered, a wave of depression was evoked and spread only within *the hemisphere where the crossed responses were being recorded.* When the depression reached the observed region the responses, together with the spontaneous activity, were depressed in much the same

way as already described for the sensory responses to touch. Figure 9 I illustrates a typical experiment. If, while a series of single shocks was being delivered, a wave of depression was started in *the stimulated hemisphere* and did not spread to the opposite side, the results were as follows. When the depression reached the region of the stimulating electrodes, the responses recorded from the opposite hemisphere became progressively smaller and after an interval of half a minute or so they were not recognizable. They reappeared a little later and gradually grew to reach their original magnitude after a few minutes. In this case, as opposed to the previous one, depression and recovery of the responses occurred while no change was noticeable in the spontaneous activity. Figure 9 II illustrates characteristic results.

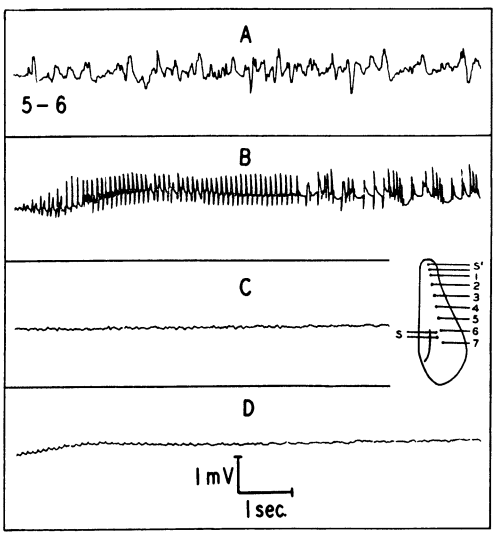

FIG. 10. Depression of tonic-clonic responses. A. Spontaneous activity. B. Tonic-clonic response following strong stimulation through electrodes S. C. Depression after appropriate weak stimulation through electrodes S′. D. Absence of tonic-clonic response when the same stimuli as in B were reapplied during the depression.

(3) *Responses of "self-sustained" type* (38) elicited by strong repetitive electrical stimulation (experimental epilepsy).—At the peak of a wave of depression, a train of stimuli which previously was effective in bringing forth a self-sustained response, might have little or no immediate effect. Figure 10 illustrates an experiment. The electrodes were arranged as shown in the inset. A brief period of repetitive electrical stimulation of adequate intensity, from the coil S, produced the response shown in B. This activity in the region of the stimulating electrodes was followed by a wave of depression which spread throughout the cortex. After complete recovery, another wave of depression was started, this time from the coil S′ and with weaker intensity of stimulation, well below threshold for the production of any after-discharge. About 3.5 minutes later, the wave reached the region of the electrodes of the coil S. When the depression was maximal there, a second stimulation from this coil was applied. The strength of the shocks and the dura-

tion of the period of stimulation were the same as before. The electrogram reproduced in D shows that no activity resulted.

I. *Depression of activity induced by drugs.* (1) *Strychnine.*—As is well known, application of strychnine to a region of the cerebral cortex leads to the local appearance of large, recurring, composite potential fluctuations. These are usually referred to as the "strychnine spikes." In a number of

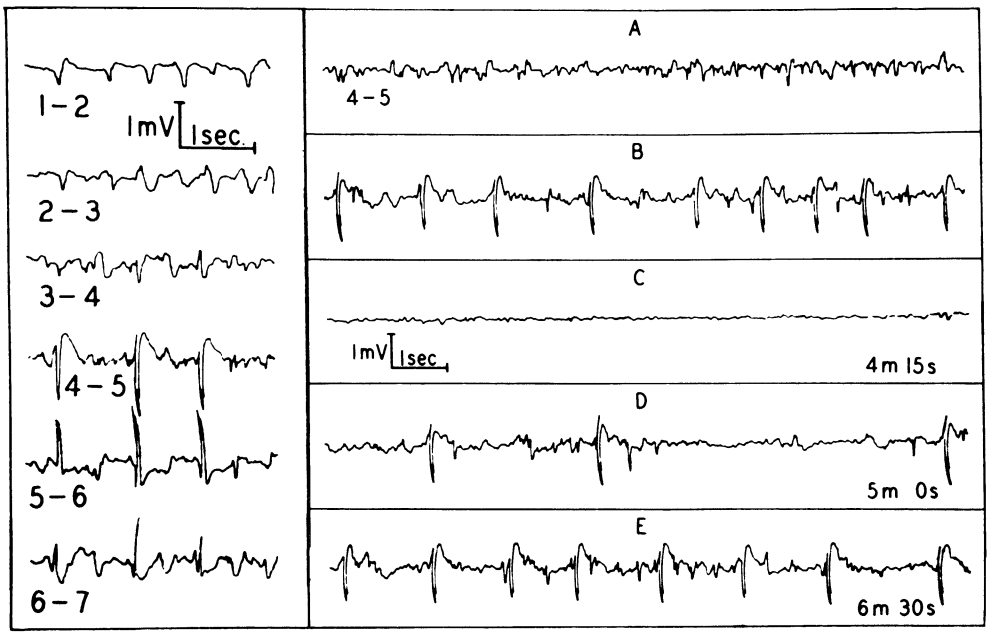

FIG. 11. Depression of the activity induced by strychnine. Electrodes arranged as in Fig. 3. Filter paper soaked in 0.1 per cent strychnine sulphate applied near electrode 5. A. Spontaneous activity. B. Strychnine spikes, record taken 7 min. after application of the drug (see also, at the left, the simultaneous records from all pairs of electrodes). C. Depression of the strychnine spikes (the depression was elicited by electrical stimulation through electrodes S). D and E. Recovery.

experiments a small piece of filter paper (about 1.5×3 mm.) soaked with a 0.1 per cent solution of strychnine sulfate was applied to the cortex close to one of the recording electrodes. Some minutes later, after the effects of the drug had developed, a wave of depression was started at a distant region. The spread past the strychninized region was followed with several pairs of electrodes. It occurred in the same manner as it did before the drug was applied. When the wave reached the treated region, the strychnine spikes, which were recurring at short intervals, became more widely spaced and promptly disappeared. None were recorded during a variable period (20 sec. to 1 min.). They then reappeared, first separated by long intervals and later (about 1 to 3 min.) with the frequency which prevailed before the depression. Figure 11 illustrates a typical observation. If the drug was applied to a wide

area and hence the spikes were present in a relatively large territory, or if the effects were too intense, then it was not possible to elicit a wave of depression which would travel within the region.

(2) *Eserine and acetylcholine.*—Many points concerning the complex effects of local applications of these drugs on the cortex of the rabbit are not well known. A study of Chatfield and Dempsey (14) revealed the existence of regional differences in the effect of local applications of these drugs to the cat's cortex. Miller, Stavraky and Woonton (35) studied the effects on rabbits but did not report regional differences. In the present observations no attempt was made to obtain an accurate description. Local applications of eserine (a small piece of filter paper, about 1.5×3 mm., soaked in 0.5 per cent eserine salicylate) resulted in most instances in a decrease of the voltages of the spontaneous activity at the treated site. This modified activity was depressed, and later recovered, when a wave of depression, started at some distance, spread past the treated region. Application of acetylcholine (0.5 per cent acetylcholine chloride), in a similar manner, to a region previously treated with eserine, led promptly to the appearance of fast, large potential waves (spikes), occurring in bursts, or, sometimes, in a more or less continuous succession. A rapid, low voltage activity was also induced. These excursions could be depressed when, following adequate stimulation a wave of depression was started at a distant region and spread to the area treated with the drugs. The depression was, as a rule, brief, electrical activity promptly reappearing. If the drugs were applied to a large extent of cortex, or if the effects were very intense, the excursions could not be depressed.

Active Electrical Phenomena Which May Occur During Depression of Spontaneous Activity

Electrical activity of various types, but always clearly different from the spontaneous activity, was often observed during the period of depression in various cortical regions. This activity was usually more prominent when the hemisphere had been exposed for some time or when it had been repeatedly stimulated, particularly if strong stimuli had been used. Although activity of this sort might appear in any region of the cortex, it was, as a rule, less intense and less frequently seen in the more frontal regions. Some of the potential waves that occurred during the period of depression of the spontaneous activity had characteristic features and could be easily identified.

A. *Slow potential waves.* Large, slow, negative waves were the most common of the several types of activity. In the course of each wave one of the recording electrodes became negative with respect to others placed on the pial surface, 1.5 to 3 mm. away. Thus, in Fig. 12A, electrode 5 became negative with respect to electrodes 4 and 6. No potential change was recorded between electrodes 4 and 3 or 6 and 7. The event is therefore localized to cortical elements in the neighborhood of lead 5. Because of their large amplitude and long duration, as compared to the excursions of the spontaneous activity, these waves were markedly distorted in some of the electrograms. They were

distorted in amplitude because correction of this distortion would have rendered the spontaneous excursions so small that changes in them would have been difficult to recognize. They were also noticeably distorted in phase when the time constant of 0.15 sec. was used for the amplifiers. With the longer time-constant of the amplifiers (0.5 sec.) and with reduced amplification an adequate record could be obtained. Such a record is shown in Fig. 12B; and

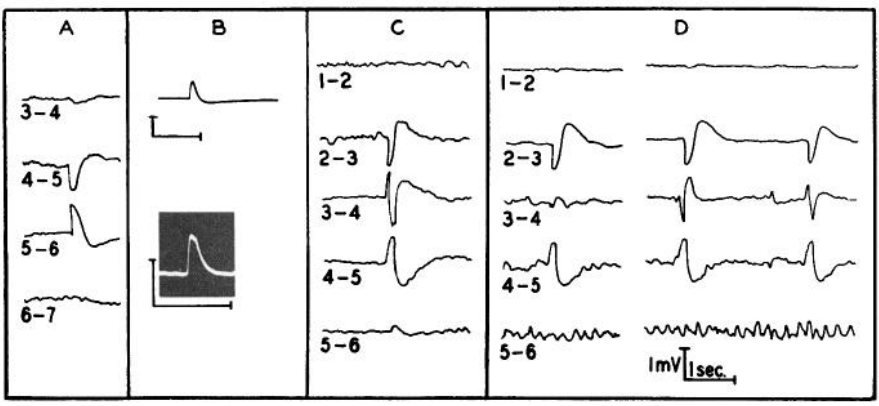

FIG. 12. Slow negative waves. Upward excursions denote negativity of the more frontal electrode (lower number) with respect to the more occipital electrode (higher number). Depression spreading from the frontal to the occipital regions. In A, C and D the electrodes were arranged in a row in the fronto-occipital direction at distances of 2 mm. A. Since leads 3–4 and 6–7 do not show any deflections, the wave recorded by 4–5 and 5–6 corresponds to a local change at 5. B. Upper record: ink-writing oscillograph with large coupling condensers in the amplifiers (calibrations—voltage: 3 mV; time: 1 sec.). Lower record: cathode ray oscillograph and direct-coupled amplifiers (calibrations—voltage: 2 mV; time: 1 sec.) C. Asynchronism of slow waves at two neighboring electrodes. Negative waves occurred at electrodes 3 and 4 (leads 2–3 and 4–5 are unaffected). The asynchronism is shown by the diphasic record 3–4. The wave at 3 preceded slightly that at 4. D. Changes in the starting point of negative waves at neighboring electrodes (3 and 4). The first discharge was synchronous, as shown by the absence of any significant deflection in record 3–4. The break in the records corresponds to a 4 sec. interval. The last two waves are asynchronous—first electrode 4 leads (the diphasic wave in 3–4 begins downwards), then electrode 3 leads (the diphasic wave 3–4 starts upwards).

an electrogram with no distortion, taken with a direct-coupled amplifier and a cathode-ray oscillograph is included for comparison. The records show the typical quick development of the negativity, and its slower subsidence. The slow negative waves appeared in any region of the cortex as soon as the spontaneous activity was depressed there. They occurred in variable number, one, a few separated by long intervals, or a rapid series lasting for 20 or more seconds. They then disappeared from this region. As the peak of the wave of depression successively reached different parts, the waves appeared successively in these different regions. Figure 13 shows that, as depression spread from electrode 1 to electrode 7, the slow excursions were recorded at different times at each of the electrodes. Figure 14 illustrates a typical group of slow negative waves in one region.

An individual slow wave could be recorded from several electrodes placed within the cortical region where they were occurring. As the electrograms in Fig. 12C show, the negativity did not develop simultaneously in all places. First, electrode 3 went negative with respect to electrodes 2 and 4, and later electrode 4 went negative with respect to electrodes 3 and 5. This indicates

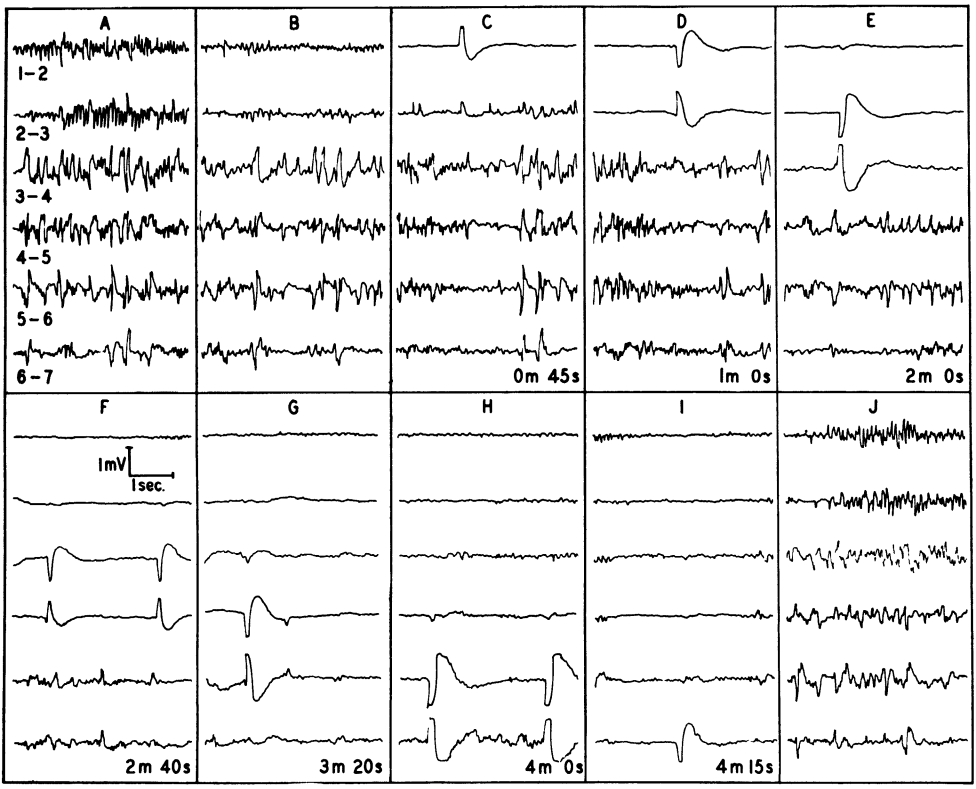

FIG. 13. Slow negative waves occurring successively in different regions as the peak of the wave of depression successively reaches these regions. Electrodes arranged as shown in the inset of Fig. 3. A. Before stimulation. B. Immediately after stimulation. J. 10 min. after I (see legend of Fig. 3, for additional explanation).

that the negativity originated at a certain focus, and spread from this focus for a few millimeters. The electrograms in Fig. 12D illustrate in addition that there was not a fixed focus, inside the region, from which the waves always started when they were recurring. In the second wave, Fig. 12D, electrode 4 became initially negative, and, in the third wave, it was electrode 3 which became negative first. In the first wave, the negativity developed almost simultaneously at electrodes 3 and 4; no large deflection was recorded between these two electrodes, while 3 was negative with respect to 2, and 4 was negative with respect to 5. Although the active zone was moving over

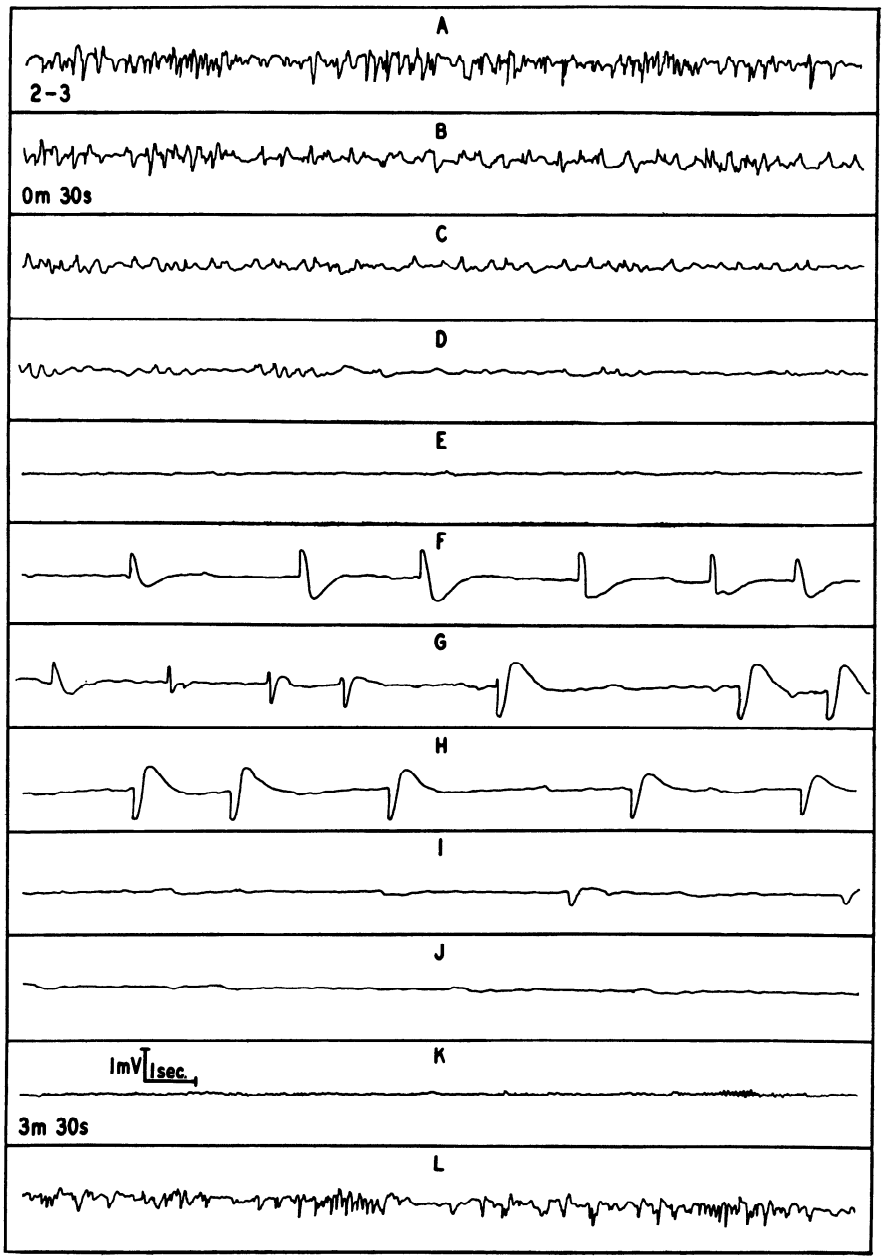

FIG. 14. A typical group of slow waves in one region. Electrodes arranged as in Fig. 3 and 13. A. Spontaneous activity. B to J. A continuous record, starting 30 sec. after stimulation, and showing the slow negative waves. K. Beginning of recovery (in the interval, about one-half min., between J and K the record was in as J). L. Recovery, 15 min. later. Compare strips F and H of this figure with D and E of Fig. 13.

the cortex in the direction of the spread of the depression, the successive initiating foci inside this zone were irregularly distributed.

As depression spread over the cortex, negative slow waves, if they did appear, they did not necessarily appear successively in all regions involved. They commonly took place only in some regions, or they might also be present in two distant regions, while the remainder of the cortex showed only

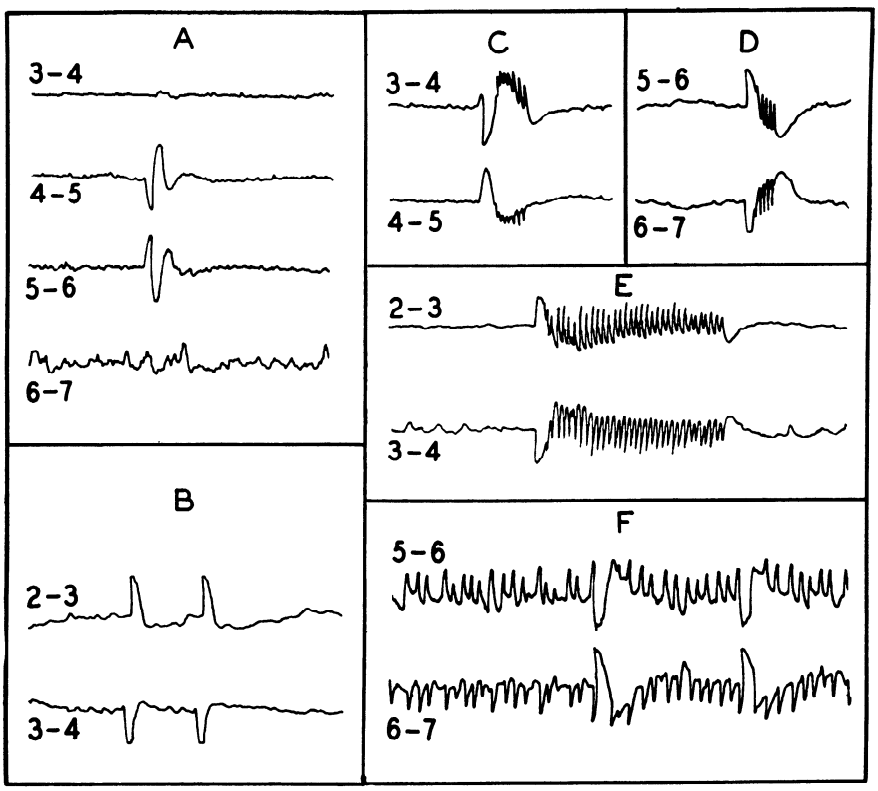

FIG. 15. A. Diphasic wave at electrode 5. B. Positive waves at electrode 3. C. Burst of spikes following a slow negative wave. D. Burst of spikes following a slow positive wave. E. Long series of spikes, following a positive wave. F. More or less continuous series of spikes, and negative slow waves.

depression. This indicates that the initiation of this activity depends on local conditions.

Single shocks applied to the pial surface of a region during the time in which negative slow waves were occurring there, could elicit responses entirely similar to these waves. Shortly after a spontaneous wave, however, single shocks always failed to elicit another one. If repeated at a frequency not much different from that at which the waves were recurring, the single shocks could control their rate of appearance, and also apparently prolong

this type of activity. Sensory stimulation could likewise "drive" (39) the slow waves in the corresponding receiving areas.

No point was found on the pial surface that was positive with respect to a distant electrode while a negative wave was recorded from a neighboring point (1). As long as the negative phenomenon did not spread from one electrode to another, interelectrodal distance did not affect the features of the waves in the records. These facts may suggest that the active elements are probably oriented perpendicularly to the surface.

In some cases, diphasic or more complex slow waves were recorded under conditions which showed that the pattern was not caused by activity spreading from one electrode to another. Slow positive potential waves were also recorded in many experiments (Fig. 15A and B). As a rule, however, these waves appeared only when the activity occurring during the depression of the spontaneous pattern was more intense, *i.e.*, when it consisted of a more or less continuous, irregular succession of large slow deflections, or when fast potential waves were also present.

B. *Fast potential waves.* The slow potential waves described in the preceding section were, in many cases, followed immediately by rapid, spike-like potential changes. These spikes were usually "positive." They occurred in bursts, as shown in Fig. 15C, D and E. On other occasions, spikes appeared in the intervals between the slow waves in a somewhat continuous succession (Fig. 15F). In many instances, finally, only a series of spikes, and no slow waves, was seen during the depression of the spontaneous activity.

When, in one region of the cortex, slow waves and spikes occurred in rapid succession, a variety of complex patterns resulted (Fig. 16 and 17). It was then sometimes really impossible to distinguish slow waves and spikes; waves of many different shapes, amplitudes and durations were recorded. In these cases, especially because the recovery of the spontaneous activity was usually prompt, it would be inappropriate to speak of depression in the corresponding region. In other regions, however, reached by the same wave of depression, before or after the particular region where intense activity occurred, only reduction of the spontaneous activity, or reduction and a few slow waves, was seen. Intense activity was very rarely present at the frontal regions; it was more frequently seen in the posterior half of the hemisphere. In a few instances activity was so marked in most regions, and the spontaneous pattern was recovered so quickly, that rather than a depression what was seen was a traveling band of modified activity: the regions in front of this band had their "normal" spontaneous background, the regions immediately behind it were somewhat depressed, those further behind showed a well-recovered normal pattern. The rate of travel of this band was about the same as when only depression of the spontaneous activity occurred.

If the stimuli used were well below threshold for the production of an electrical after-discharge, the occurrence of slow waves or other activity in a given region was the same regardless of where the wave of depression was started. The regional effects of a spreading depression of the spontaneous

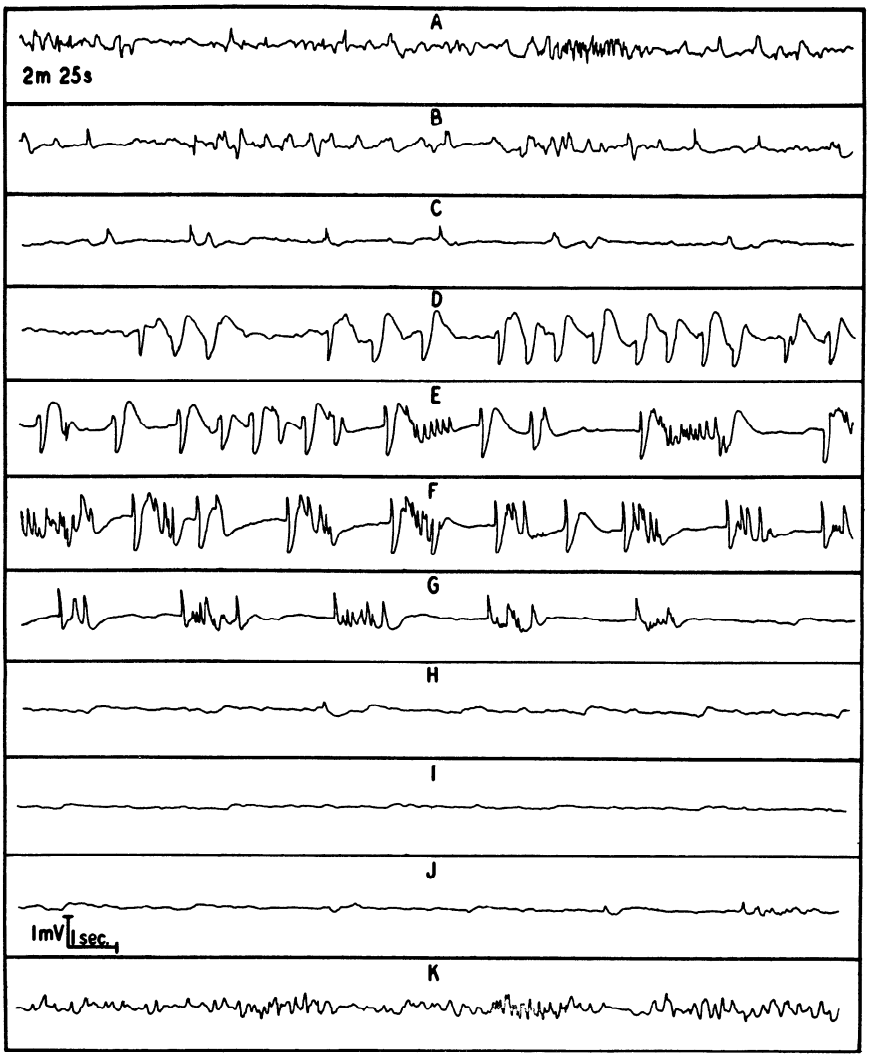

FIG. 16. Intense activity occurring when the spreading depression reaches a given region. A to J. Continuous record, beginning 2 min. 25 sec. after a distant stimulation that elicited a depression. K. Recovery, 5 min. later.

activity, in one animal, at a given time, were similar for a number of successive stimulations. Variability was found from animal to animal. Striking variability also took place, as a rule, in the course of a given experiment—more activity was seen during the periods of depression when the hemispheres had been exposed for several hours and stimulated repeatedly.

C. *Activity similar to "self-sustained" (tonic-clonic) responses of experimental epilepsy.* When the activity attending depression was intense it followed, in many cases, a course quite similar to that of the discharges that

follow a period of a few seconds of strong stimulation of the cerebral cortex. Figure 18 illustrates this similarity (38). This is a typical "tonic-clonic" discharge, but it is important to emphasize that the stimulated region and the intervening areas did not share in the self-sustained activity recorded. In the

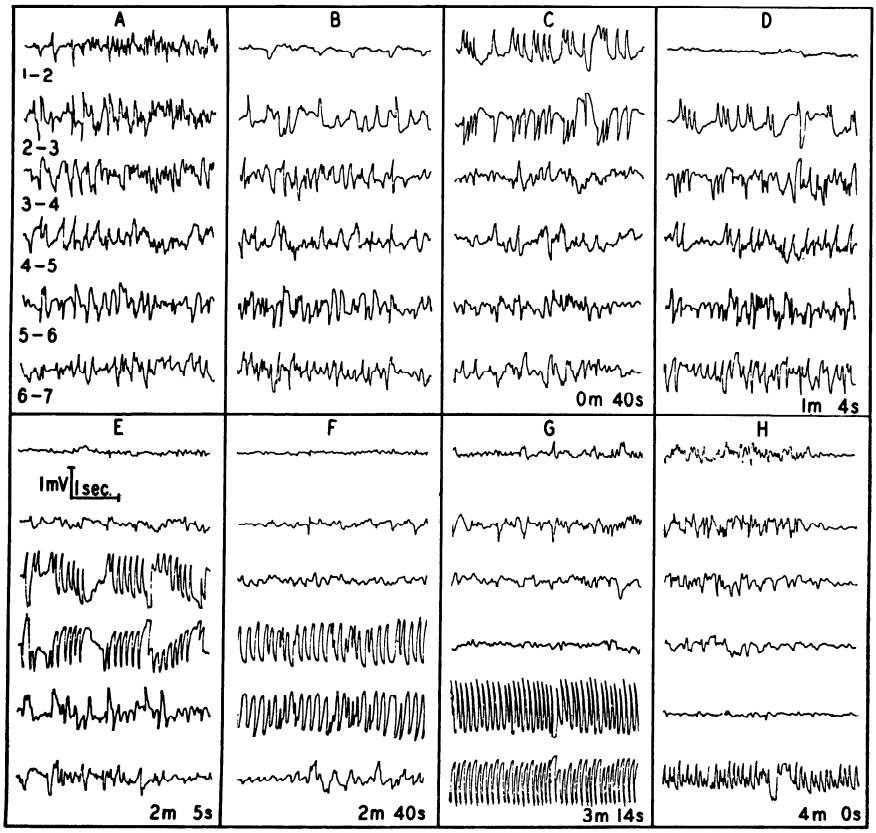

FIG. 17. Very intense activity associated with depression, occurring in all regions tested. Electrodes arranged as in Fig. 3. A. Before stimulation. B. Immediately after stimulation. The discharges in electrodes 5 and 6 resemble typical tonic-clonic sequences.

stimulated region and the intervening areas there was only depression of the spontaneous activity (and some isolated slow waves). The self-sustained discharge might appear only three or more minutes after stimulation if the stimuli were applied to a distant region. These discharges were usually seen in the posterior half of the hemisphere. They were, like the slow waves, limited at a particular time to a certain region of the cortex, and if they moved to another region, the rate of travel was the same as that of the slow waves (*i.e.*, the same as that of the depression of the spontaneous activity).

That the self-sustained activity was not a direct consequence of the stimuli, but an indirect effect caused by the mechanism of depression, was

also indicated by the following observations. In some animals an area was found which exhibited self-sustained discharges when a distant point was stimulated. Then that area was stimulated locally with sufficiently strong shocks. A first self-sustained response was followed after an interval of several seconds by a second similar discharge. This second period of activity coincided with the initiation of a typical spreading wave of depression. Thus

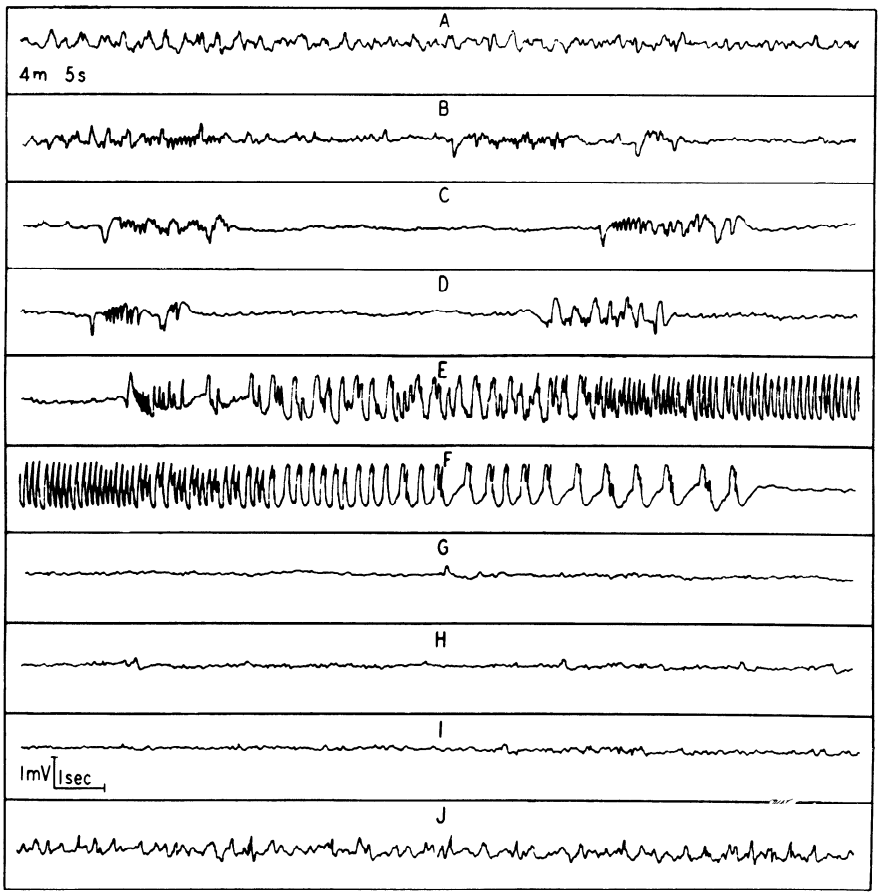

FIG. 18. Electrodes, etc. as in Fig. 16. The activity here is quite similar to a typical tonic-clonic response. A to I. Continuous record. J. Recovery.

it appears that the first period of activity was a direct response, but the second was an indirect effect, consequent upon the process responsible for the depression (Fig. 19).

OTHER ANESTHETICS; EXPERIMENTS ON PIGEONS AND CATS

With rabbits under nembutal the results were quite similar to those obtained with dial. The same was true when chloralose was used. On the other

hand, in animals under ether, responses of the type described were obtained only when the anesthesia was very light, inadequate for prolonged observations.

In pigeons (nembutal) a spreading depression of the spontaneous electrical activity was easily obtained. The process had the same general features as described for the rabbit. The electrodes were placed on the dorsolateral wall of the hemisphere. A survey of their position with relation to the

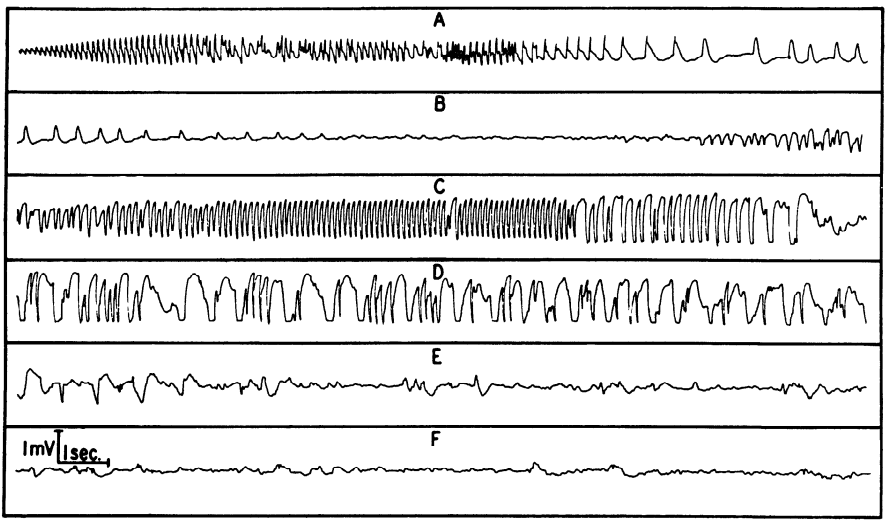

FIG. 19. Immediate and late tonic-clonic responses to local strong stimulation. The stimulating electrodes were about 2 mm. away from the recording leads. A to F. Continuous record, starting immediately after the stimulus. The second period of activity coincided with the initiation of a typical spreading wave of depression.

various cortical or corticoid areas that have been recognized in the avian brain (29) has not yet been completed.

A spreading depression of the electrical activity was also observed in the few experiments made on cats. As in the rabbit, large slow potential waves appeared in many instances during the depression. In these few experiments stimulating and lead-off electrodes were placed along the suprasylvian gyrus. In almost all the animals the brainstem had been transected under ether and the anesthetic then discontinued.

DISCUSSION

The data are not yet sufficient for an adequate discussion of the subject. Some surmises, concerning the changes in cortical function which might lead to the depression and the factors which might intervene for its spread, may be considered. These surmises are of value in that they suggest future interesting experiments.

The term "inhibition" has been used to cover many, probably heterogeneous, central phenomena. It has also acquired several specific interpretative connotations. For these reasons this term was avoided, and the purely descriptive word "depression" was selected.

The close relations between the spreading depression and the discharges of experimental epilepsy may first be stressed. On page 377 it was pointed out that typical discharges of experimental epilepsy may occur in a cortical region when it is reached by a spreading wave of depression, and that in certain cases such discharges take place successively in different regions as the wave of depression reaches them. Indeed, as a rule, whatever the type of activity that appears during depression, some features or properties of the tonic-clonic discharges (38) may be recognized. It may be said that the electrical events are always of a "convulsive" character.

The most frequent and simplest type of activity consists (page 376) of large, slow potential waves. When these waves recur in one region, this recurrence exhibits features similar to those of the repetitive clonic bursts of the cortical responses of experimental epilepsy. During the clonic bursts (1, 38), the regions inside the active area are coupled, *i.e.*, activity in one is promptly followed by activity in the others (synchronism of the clonic bursts), but there is not a systematic pacemaker—the bursts originate at different, irregularly distributed points. A similar situation may be recognized inside the depressed cortex in which slow waves are recurring. Here also, activity starts at different points and is immediately followed by discharge in others inside the region involved. The conditions for driving the slow waves with single electrical shocks applied to the region follow the same general rules which govern the driving of the clonic bursts (39). The slow waves, as well as the spikes that may accompany them, show at times a striking resemblance to isolated components of the clonic phase of the self-sustained responses as described by Rosenblueth and Cannon (38). The slow waves are similar to their component IV, and the spikes to component III—the two components usually associated in the clonic bursts. Therefore, it seems reasonable to infer that the different types of activity which may appear during depression are closely related to each other and to the tonic-clonic responses. The differences seen in various instances are mainly quantitative.

There are two fundamental facts about the cortical discharges of experimental epilepsy which should be mentioned at this point. First, rapid excision of the stimulated area does not stop the response and does not prevent further spread (see Munk, in Wernicke [40]; 13, 25, with regard to motor convulsions; and 38, with regard to the electrical phenomena of the cortex). This fact indicates that the area stimulated starts, but does not remain in control of the response and its spread. In the response studied here the stimulated area may return to its normal spontaneous activity, after a period of depression, at a time when depression is starting at some distant region. This indicates that here also the stimulated region initiates the response, but

that the progress of the spreading depression is not controlled by an enduring influence from this region.

The second noteworthy fact about the tonic-clonic responses is that the course of the activity is similar in any of the several regions to which it may spread, including the region stimulated. With regard to motor convulsions, François-Franck and Pitres (25) noted that, "dans l'ensemble de l'attaque, chaque membre . . . fait independamment des autres membres, une phase tonique et une phase clonique." Rosenblueth and Cannon (38) found that the electrical discharges in any cortical region start with the first, rapid component of the responses, and then pass into clonic bursts coupled with those in the rest of the active cortex. This fact indicates that the response starts anew in any cortical region, much as in the region stimulated. These authors stated that, "it is not necessary to assume that other elements than those which yield component I are involved in the spread of the responses, since activity of any area always starts with this component." Similarly, the time course of the spreading depression is the same in all regions involved, *i.e.*, the response again starts anew in distant places in much the same manner as in the area stimulated.

Rosenblueth and Cannon (38) observed that in any region along the spread of the cortical epileptic discharges, "the responses are usually preceded and attended by inhibition of the spontaneous activity." This observation supports the close relationship between the spread of the depression and that of the tonic-clonic activity. In the monkeys studied by Rosenblueth *et al.* 38,39) the spread of the cortical tonic-clonic electrical activity, induced by electrical stimulation, took place more readily in the backward than in the forward direction in one hemisphere. Similarly, in the rabbit's brain, spread of the depression of the spontaneous electrical activity was more readily obtained when the frontal regions were stimulated than when the stimuli were applied to regions near the occipital pole.

From all these facts it is inferred that the mechanisms of spread of the waves of depression and of tonic-clonic activity involve the same cortical elements. It is also inferred that depression and tonic-clonic activity are closely related, *i.e.*, the elements which cause depression and its spread may in appropriate conditions activate the elements involved in the tonic-clonic responses of experimental epilepsy. A corollary of these inferences is that *the spread of tonic-clonic activity may be produced by the elements which cause the initial depression, rather than by those responsible for component I.*

A closer consideration of the inferred correlation of the two responses cannot be made at present. Thus it would be important to determine if the rate of spread of depression and that of tonic-clonic activity are the same in a given animal, under comparable conditions. Spread of tonic-clonic cortical activity has been studied in monkeys (23, 38). Whether in this species a spreading depression can be produced is still to be determined. In narcotized rabbits, typical gradual spread of tonic-clonic cortical activity out from a small area strongly stimulated for a few seconds, and resulting finally in a

prolonged synchronous clonic activity over a wide extent of cortex, is not obtained. For this reason the comparison of the rates of spread of tonic-clonic activity and of depression could not be carried out.

It is interesting to note that the results in pigeons, as well as those in cats (when the brainstem had been transected), were essentially similar to those obtained in rabbits. It is likely, therefore, that species differences may not be prominent and that the anesthetic may not markedly influence the phenomenon.

The fact that the depression may not spread beyond a narrow band of cocainized tissue, and also that it does not spread to the retrosplenial area, seem to point to a neuron-to-neuron mechanism for the spread. It is possible that some elements are stimulated by the electric shocks, and that the activity of these elements results in inhibition of the activity of many other neurons. A wave of marked vasodilatation and increased blood flow travels over the cortex simultaneously with the wave of depression (32). The most likely mechanism by which the response of the pial vessels might be produced seems to be a release into the interstitial fluids of some chemical vasodilator. Whatever the mechanism of this vasodilatation, it is to be expected that the marked increase in blood flow will in turn influence the activity of the cortical neurons in the region concerned. That is, the increased flow might, for instance, lower the carbon dioxide tension and, therefore, alter the functional activity of the nervous elements (28, 33). The time course of the depression of the spontaneous electrical activity in a given region is therefore probably affected by this mechanism. Also, it is possible that the chemical vasodilator itself, or some other chemical released in the tissue fluids, alters the activity of the nervous elements and so conditions directly the time course of the depression in any given region. A lack of mutual excitatory facilitating interaction among a group of elements, if some of them were inactivated, might also have a part in the development of the depression.

If the initiation and spread of the depression are due to the discharges of certain elements, then these discharges should have electrical signs. Hence it would be expected that some specific change in the electrical activity should be manifest at the front of the wave of depression. There was no evidence of such change in the records. It is necessary to assume therefore, that the active elements are distributed irregularly in the cortex, with no definite spatial orientation in relation to the electrodes, so that their discharges do not set up a recordable potential difference between the electrodes, *i.e.*, the units of electrical activity may largely cancel each other. The complexity of the cortical structure permits such an assumption. The spread of depression may then be accounted for by synaptic activation of similar elements in adjacent regions. This interpretation implies that active depressing elements should be present in all cortical regions to which depression spreads. The fact that a wave of depression may be started at any of those regions supports the interpretation. The slow propagation, a difficult point to explain on the basis of synaptic activation of adjacent elements, might be due to the need

of summation of excitation over a long period of time before new elements are activated. Since the spread within one hemisphere is to the regions in the vicinity of a given depressed area, it should take place mainly through short neuronal connections. On the other hand, the fact that the effect can be elicited in the contralateral hemisphere seems to indicate that long pathways may be involved.

During the development of depression in a region not only was the spontaneous activity decreased, activity which in itself is to be regarded as a sum of components (17, 36) but in addition may different types of cortical responses were eliminated. This may be considered evidence that there exists in the cortex a mechanism for a diffuse inhibitory influence. Changes in the physico-chemical composition and equilibria in a given depressed region, as seemingly evidenced by the changes in the pial vessels and as probably brought forth by the marked and sudden increase in blood flow, may have an important part in the realization of this diffuse cortical inhibition. They might account for the fact that a second spreading depression cannot be elicited from the same region until the recovery of the electrical activity is well advanced there.

The depression illustrated in Fig. 11 II may be singled out, in that decrease of response appeared when a wave of depression reached not the responding but the stimulated region. It is possible that depression may decrease the electrical excitability of cortical elements. On the other hand, it is unlikely that the excitability of the callosal fibers should be modified. Probable explanations are that the stimuli act on the cell bodies of the projecting neurones, but that their threshold had been elevated, or else that the stimuli activate directly other elements than the projecting neurones.

Several of the ipsilateral responses that can be obtained by direct cortical stimulation with single shocks were studied by Adrian (1) and by Rosenblueth and Cannon (38). These responses exhibit several components with different features. This complexity suggests that several different sets of elements may be involved. A detailed study of the depression of these responses, with different positions of the stimulating and recording electrodes in relation to the direction of spread of depression, so that either the stimulating or the recording pair is reached by the depression, one slightly before the other, should contribute significantly to their understanding, and to that of the mechanism of depression. The observations made here (page 384) are considered only an introductory step in this study.

The depression of tonic-clonic responses is difficult to explain. Spreading depression may cause the appearance of tonic-clonic activity. The two phenomena are closely related, yet in certain conditions depression opposes the initiation of a tonic-clonic response.

Some of the data presented in the preceding pages may have a bearing on the interpretation of some of the potential waves recorded from the surface of the hemispheres. Forbes and Morison (24) and Adrian (2) suggested that the initial "positive" component of the sensory responses did not result from

activity in cortical neurons, but that it was due to potential gradients in afferent fibers from the thalamus. One fact supplying evidence of this origin of the positive waves was that similar waves could be recorded from the exposed white matter after removal of the cortex. Curtis (16) interpreted the early "positive" wave of the responses evoked in the opposite hemisphere by single shocks applied to the pial surface, as due to summation of axon spikes of the callosal fibers. As opposed to the view that these potentials are originated entirely in the afferent axons, a view shared also by Marshall, Woolsey, and Bard (34), more recently Dempsey and Morison (17) obtained evidence that cortical elements contribute to the initial positive wave of the sensory responses. The depression of these responses and of the responses to single shocks applied to the contralateral hemisphere is difficult to reconcile with the view that the initial positive wave is the manifestation of potentials in the corticopetal fibers (thalamic or callosal). It is quite unlikely that axon potentials (in the paths approaching the cortex) could be depressed or inhibited. The depression seems to indicate that the activity revealed by these positive waves corresponds to some cortical neurons. If the arrival of corticopetal impulses should record, with electrodes on the pial surface, as a positive potential this potential would be much briefer and smaller than the initial positive component of the typical records.

A second comment suggested by the present data concerning the interpretation of electrocorticograms is the following. Adrian and Matthews (3) concluded that the slow potential waves recorded from the cortex are summated effects built up from an asynchronous series of brief pulsations in nerve cells. One of the arguments they presented for the composite nature of slow waves was that the origin of those waves could not be localized. The records presented in Fig. 14 show that it is possible to localize the origin of the specific slow negative waves that may appear as depression reaches a cortical region. It is likely therefore that these waves are not composed from brief asynchronous discharges in elements distributed over a wide area. These waves might represent prolonged potential changes in relatively few elements or else they might have an origin of an entirely different nature.

There is obviously a similarity between the response described in the present study and the phenomenon of "suppression" of the electrical activity, described first by Dusser de Barenne and colleagues (4, 19–22, 26, 27). There are, however, many differences between the two responses. Suppression of the electrical activity in the experiments of these authors is brought about by the influence of specific cortical areas on the activity of the nucleus caudatus, which in turn by way of the thalamus influences the activity of the cortex. In the present experiments the evidence indicates that the characteristic spread is a cortico-cortical process. In addition, since the gradual spread progresses uniformly, since the same events repeat in each cortical region, and since there is no correlation in time of the events at distant points with those at the stimulated area, it is clear that the mechanism responsible for depression is widespread over the cortex rather than the attribute of spe-

cific areas. A further difference is that specific electrical activity often occurs during depression. No such activity has been reported in the suppressed cortex. A closer comparison of the two responses awaits further studies.

I wish to express my cordial gratitude to Dr. Hallowell Davis. This study was developed under his continuous, valuable and friendly supervision. My daily contacts with Dr. Arturo Rosenblueth, who followed the experiments closely, were a decisive factor in the completion of this work. In all its phases, his help was beyond estimation.

Summary

In rabbits, under dial narcosis, weak faradic or mechanical stimulation of the exposed cerebral cortex elicits a characteristic response designated "spreading depression."

Shortly after the stimulation the spontaneous electrical activity decreases markedly at the stimulated region (Fig. 1). The depression then slowly spreads in all directions, successively affecting adjacent areas. Within 3 to 6 minutes it involves all of the dorsolateral cortex, except the area retrosplenialis granularis dorsalis (Rsg β, of Rose) (Fig. 2–5). The depression can be initiated in any of the regions involved in the spread, but is usually more readily obtained from the frontal than from the occipital areas.

Recovery of the initial pattern of spontaneous activity is slow; it requires, as a rule, 5 to 10 minutes at each region. The spontaneous activity at the stimulated region is often well recovered at a time when the depression is just starting in distant parts. If only weak stimuli are used, depression at any region runs the same course regardless of what region is stimulated.

Only with supraminimal stimulation does the depression spread to the opposite hemisphere, then appearing first in the region symmetrical to the point of stimulation and thence spreading as in the stimulated hemisphere.

The spreading depression affects not only the spontaneous electrical activity, but also several cortical responses; *i.e.*, responses to touch, to electrical stimulation of afferent nerves, to illumination of the retina, to ipsilateral or contralateral cortical electrical stimulation, and to local application of strychnine or of eserine plus acetylcholine (Fig. 6–11). Single shocks applied to a depressed region fail to elicit typical responses in the opposite nondepressed hemisphere.

Specific activity, different from the spontaneous, often develops during the period of depression of a region. The most common type of this activity is composed of large, slow, localized potential waves, during which one electrode becomes negative with respect to others 1 to 3 mm. distant (Fig. 12, 13, 14). Fast components may also appear, and the activity when intense closely resembles the "seizure pattern" of experimental epilepsy (Fig. 15–19).

The depression and "tonic-clonic" activity of experimental cortical epilepsy seem to be closely related phenomena. The spread of tonic-clonic responses is probably mediated by the same cortical elements which are involved in the spread of depression. The two processes are mainly or ex-

clusively cortical, *i.e.*, they do not require a contribution from sub-cortical centers. Their development and characteristics are not determined by the stimuli, but depend on the local characteristics and conditions of the affected regions.

REFERENCES

1. ADRIAN, E. D. The spread of activity in the cerebral cortex. *J. Physiol.*, 1936, *88:* 127–161.
2. ADRIAN, E. D. Afferent discharges to the cerebral cortex from peripheral sense organs. *J. Physiol.*, 1941, *100:* 159–191.
3. ADRIAN, E. D., and MATTHEWS, B. H. C. The interpretation of potential waves in the cortex. *J. Physiol.*, 1934, *81:* 440–471.
4. BAILEY, P., DUSSER DE BARENNE, J. G., GAROL, H. W., and MCCULLOCH, W. S. Sensory cortex of chimpanzee. *J. Neurophysiol.*, 1940, *3:* 469–485.
5. BARTLEY, S. H., and BISHOP, G. H. The cortical response to stimulation of the optic nerve in the rabbit. *Amer. J. Physiol.*, 1933, *103:* 159–172.
6. BARTLEY, S. H., and BISHOP, G. H. Factors determining the form of the electrical response from the optic cortex of the rabbit. *Amer. J. Physiol.*, 1933, *103:* 173–184.
7. BARTLEY, S. H., O'LEARY, J., and BISHOP, G. H. Differentiation by strychnine of the visual from the integrating mechanisms of optic cortex in the rabbit. *Amer. J. Physiol.*, 1937, *120:* 604–618.
8. BISHOP, G. H. Cyclic changes in excitability of the optic pathway of the rabbit. *Amer. J. Physiol.*, 1933, *103:* 213–224.
9. BISHOP, G. H., and O'LEARY, J. Components of the electrical response of the optic cortex of the rabbit. *Amer. J. Physiol.*, 1936, *117:* 292–308.
10. BISHOP, G. H., and O'LEARY, J. Potential records from the optic cortex of the cat. *J. Neurophysiol.*, 1938, *1:* 391–404.
11. BREMER, F. Cerveau "isolé" et physiologie du sommeil. *C. R. Soc. Biol., Paris*, 1935, *118:* 1235–1241.
12. BRODMANN, K. *Vergleichende Lokalisationslehre der Grosshirninde.* Leipzig, J. A. Barth, 1909, 324 pp.
13. BUBNOFF, N., and HEIDENHAIN, R. Ueber Erregungs- und Hemmungsvorgänge innerhalb der motorischen Hirncentren. *Pflüg. Arch. ges. Physiol.*, 1881, *26:* 137–200.
14. CHATFIELD, P. O., and DEMPSEY, E. W. Some effects of prostigmine and acetylcholine on cortical potentials. *Amer. J. Physiol.*, 1942, *135:* 633–640.
15. CURTIS, H. J. Intercortical connections of corpus callosum as indicated by evoked potentials. *J. Neurophysiol.*, 1940, *3:* 407–413.
16. CURTIS, H. J. An analysis of cortical potentials mediated by the corpus callosum. *J. Neurophysiol.*, 1940, *3:* 414–422.
17. DEMPSEY, E. W., and MORISON, R. S. The electrical activity of a thalamocortical relay system. *Amer. J. Physiol.*, 1943, *138:* 283–296.
18. DROOGLEEVER FORTUYN, A. B. Cortical cell-lamination of the hemispheres of some rodents. *Arch. Neurol. Psychiat., Lond.*, 1914, *6:* 221–354.
19. DUSSER DE BARENNE, J. G., and MCCULLOCH, W. S. Functional organization in the sensory cortex of the monkey (*Macaca mulatta*). *J. Neurophysiol.*, 1938, *1:* 69–85.
20. DUSSER DE BARENNE, J. G., and MCCULLOCH, W. S. Sensorimotor cortex, nucleus caudatus and thalamus opticus. *J. Neurophysiol.*, 1938, *1:* 364–377.
21. DUSSER DE BARENNE, J. G., GAROL, H. W., and MCCULLOCH, W. S. The "motor" cortex of the chimpanzee. *J. Neurophysiol.*, 1941, *4:* 287–303.
22. DUSSER DE BARENNE, J. G., GAROL, H. W., and MCCULLOCH, W. S. Functional organization of sensory and adjacent cortex of the monkey. *J. Neurophysiol.*, 1941, *4:* 324–330.
23. ERICKSON, T. C. Spread of the epileptic discharge. An experinental study of the after-discharge induced by electrical stimulation of the cerebral cortex. *Arch. Neurol. Psychiat., Chicago*, 1940, *43:* 429–452.
24. FORBES, A., and MORISON, B. R. Cortical response to sensory stimulation under deep barbiturate narcosis. *J. Neurophysiol.*, 1939, *2:* 112–128.
25. FRANÇOIS-FRANCK, C. A., and PITRES, A. Recherches expérimentales et critiques

sur les convulsions epileptiformes d'origine corticale. *Arch. Physiol. norm. path.*, 1883, *15*(II): 1–40 and 101–144.
26. GAROL, H. W. The "motor" cortex of the cat. *J. Neuropath. exp. Neurol.*, 1942, *1:* 139–145.
27. GAROL, H. W. The functional organization of the sensory cortex of the cat. *J. Neuropath. exp. Neurol.*, 1942, *1:* 320–329.
28. GERARD, R. W. Factors controlling brain potentials. *Cold Spg. Harb. Symp., Quant. Biol.*, 1936, *4:* 292–304.
29. KAPPERS, C. V. A., HUBER, G. C., and CROSBY, E. C. *The comparative anatomy of the nervous system of vertebrates, including man.* New York, Macmillan, 1936, 2 vols.
30. KORNMÜLLER, A. E. Die bioelektrischen Erscheinungen architektonischer Felder der Grosshirnrinde. *Biol. Rev.*, 1935, *10:* 383–426.
31. KORNMÜLLER, A. E. *Die bioelektrischen Erscheinungen der Hirnrindenfelder.* Lpz., G. Thieme, 1937, 118 pp.
32. LEÃO, A. A. P. Pial circulation and spreading depression of activity in the cerebral cortex. *J. Neurophysiol.*, 1944, *7:* 391–396.
33. LENNOX, W. G., GIBBS, F. A., and GIBBS, E. L. The relationship in man of cerebral activity to blood flow and to blood constituents. *Res. Publ. Ass. nerv. ment. Dis.*, 1938, *18:* 277–297.
34. MARSHALL, W. H., WOOLSEY, C. N., and BARD, P. Observations on cortical somatic sensory mechanisms of cat and monkey. *J. Neurophysiol.*, 1941, *4:* 1–24.
35. MILLER, F. R., STAVRAKY, G. W., and WOONTON, G. A. Effects of eserine, acetylcholine and atropine on the electrocorticogram. *J. Neurophysiol.*, 1940, *3:* 131–138.
36. MORISON, R. S., and DEMPSEY, E. W. A study of thalamo-cortical relations. *Amer. J. Physiol.*, 1942, *135:* 281–292.
37. ROSE, M. Cytoarchitektonischer Atlas der Grosshirnrinde des Kaninchens. *J. Psychol. Neurol., Lpz.*, 1931, *43:* 353–440.
38. ROSENBLUETH, A., and CANNON, W. B. Cortical responses to electric stimulation. *Amer. J. Physiol.*, 1942, *135:* 690–744.
39. ROSENBLUETH, A., BOND, D. D., and CANNON, W. B. The control of clonic responses of the cerebral cortex. *Amer. J. Physiol.*, 1942, *137:* 681–694.
40. WERNICKE, C. *Lehrbuch der Gehirnkrankheiten.* Kassel, T. Fischer, 1881, 572 pp.