ANESTHESIA AND THE E.M.F. OF THE NERVOUS SYSTEM*

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Burge and his associates have reported on the relation of anesthesia to currents picked up from the nervous system. Burge, Neild, Wickwire, and Orth[2] connected the cortex and sciatic nerve of a dog to a sensitive galvanometer by non-polarizable electrodes and reported the following phenomena. The cortex of the dog, deeply anesthetized with ether, was found to be electropositive to the sciatic nerve, a current of from 2 to 3 microamperes having been recorded. As the animal recovered from anesthesia, however, "the cerebral cortex became progressively less electropositive." Eventually a reversal of polarity was observed which produced a current of from 2 to 3 microamperes (brain negative) in a lightly anesthetized preparation. In addition to experiments with ether, Burge, Wickwire, and Schamp[3] have studied the effects of chloroform, nitrous oxide, ethylene, alcohol, nembutal, morphine, carbon dioxide, hemorrhage, and asphyxia. They believe the cortex of the conscious animal to be always negative to the sciatic nerve and that agents which decrease the activity of the cortex decrease this negativity. Hence, all the anesthetics tested made the cortex electropositive. With nembutal and morphine it was found necessary to use several times the anesthetic dose to produce positivity. To quote the authors, "In fact such large doses were used in the experiment that the animals died from the effects of the drug." Recently, Burge, Koons, and Burge[1] have reported electrical changes in the dorsal and ventral spinal nerve roots in etherized dogs. In deeply anesthetized dogs a current of 0.09 microamperes flowed from the dorsal to the ventral root. "As the dog came from under the ether the strength of this current gradually decreased to zero. With further recovery there was a reversal of polarity, and when the dog was only slightly anesthetized a current of 0.06 microamperes flowed from the anterior to the posterior root thus showing the posterior root to be electronegative in the semi-conscious dog."

* This is part of a dissertation submitted to the Faculty of the Graduate School of Yale University in partial fulfillment of the requirements for the degree of Doctor of Philosophy. The research was aided by a grant from the George H. Knight Memorial Fund. From the Section of Neuro-Anatomy, Department of Anatomy, Yale University School of Medicine.

These results point to a connection between the level of activity of the nervous system and its electrical output. Confirmation of the results should be especially desirable in view of their theoretical importance and, further, since the description given of the experiments is somewhat meager in certain respects. Nowhere is a more complete description of the apparatus given than that a sensitive galvanometer and non-polarizable electrodes were used. In the paper of Burge, Neild, Wickwire, and Orth[2] rats, turtles, and frogs are described as experimental animals in addition to dogs. Yet all the results reported are based on experiments performed on dogs and the reader is left to assume that the results were the same in all animals investigated. In lower vertebrates, such as the frog, it would be desirable to know where the electrodes were placed if Burge's general thesis on the electronegativity of the unanesthetized cortex was tested. The chief difficulty in evaluating the experiments lies in the method of measurement. One may reasonably assume that the galvanometer used was of sufficient sensitivity to record the currents described. Nevertheless, galvanometric measurements are not free from external resistance changes and draw steady currents from the system measured in continuous recording. This is extremely important when the nervous system is involved. According to Mendelssohn currents of .001 milliamperes are sufficient to produce electrotonic effects and at least some of the currents measured by Burge and his co-workers exceed this figure.

The apparatus described by Burr, Lane, and Nims[4] should be admirably adapted to the study of constant currents in the nervous system. The voltmeter (described in detail in the paper of Burr, Lane, and Nims) is stable, adjustable to microvolt sensitivity, relatively independent of external resistance changes, and draws current of only 10^{-10} amperes with a millivolt input. This instrument has been rigorously tested over a period of years and has proved satisfactory for biological material in both the millivolt and microvolt range of sensitivity.

The following experiments, undertaken at the suggestion of Professor Burr, are concerned with the investigation of the effect of anesthesia on the E.M.F. of the nervous system. A description of materials and methods follows.

The electrodes used in the present experiments were silver-silver chloride prepared as described by Burr, Lane, and Nims[4] and adjusted so that they did not differ by more than 200 microvolts. A

correction was made for this difference at each reading. The electrodes were connected to the animal by isotonic salt bridges contained in glass tubing. The tips of the tubing in contact with the preparation under consideration were drawn to fine bore and placed directly against the surface of the nervous system by micro-manipulation. Possible pressure effects were further excluded by substitution of string wicks which connected the glass tips to the nervous system. It was found in the preliminary experiments that this precaution was unnecessary so that most of the data were collected without the use of wicks.

The animals used were albino rats, and two types of experiments were carried out. In one series the changes in voltage between different parts of the central nervous system were investigated, while in the other, changes between the central nervous system and peripheral nerve (sciatic) were studied. The sensitivity of the apparatus was set so that the smallest division on the paper represented one millivolt in the input circuit. No changes of less than a millivolt are considered significant in the experiments here reported. Complete records were obtained from 37 rats,* and these form the basis for the following descriptions.

Series I: Changes in the central nervous system

Albino rats weighing between 220 and 435 gm. (average of 330 gm.) were anesthetized by intraperitoneal injections of sodium amytal or nembutal. The sodium amytal dosage was 100 mg. per kg. of body weight and the nembutal dosage was 50 mg. per kg. After the anesthetic had taken effect the animal was securely tied, dorsum up, to an animal board. The operations and experiments were carried out during the winter months in a heated laboratory whose average temperature was $24.4 \pm 2.5°C$. A gooseneck lamp was placed near the animal (at a point equidistant from the electrodes) in order to assist in the maintenance of body temperature. The animal board was separated from the table containing the measuring apparatus by glass castors and no contact between the animal and the table containing the apparatus was permitted. In a few cases where the animals were not completely anesthetized by the original intraperitoneal dosage, anesthesia was assisted with ether. The skin was shaved over the projected operative field and two mid-

*Twenty in Series I, twelve in Series II, and five controls.

dorsal incisions were made; one through the scalp, the other through the skin and fascia overlying the thoracic or upper lumbar region of the vertebral column.

The brain was exposed by cleaning the external periosteum of the calvarium with a periosteum lifter, boring several small holes through the skull with a small electrically operated drill and by stripping off the bone with small nail-clippers. The bone was removed from one or both dorsal surfaces, leaving a thin ridge of bone over the superior sagittal sinus and the sinus itself intact. The dura was picked up with a dural hook, incised with fine, sharp-pointed scissors, and reflected.

The spinal cord was exposed by cleaning the dorsal lamina of musculature with a periosteum lifter, incising the ligamentum flavum, and inserting the points of nail-clippers into the orifice so made. The laminae of three vertebrae were removed, the dura picked up, incised, and reflected.

Contact was established between the Ag-AgCl electrodes and the nervous system by means of glass tubes filled with 0.8 per cent NaCl solution. The contact tips were drawn to fine bore and the electrodes were placed by micro-manipulation. The brain electrode was placed in the center of the field prepared on either of the two hemispheres and the cord electrode was placed on the mid-dorsal surface of the spinal cord at the level of the middle vertebra of the three whose laminae had been removed.

With the dosages of anesthesia listed above, rats have begun to recover from narcosis within one hour of the administration of the drug. Hence, in most cases, continuous recordings of the voltage changes were made with the electrodes placed from approximately one hour after administration of the anesthetic until, at the latest, the animal had recovered from anesthesia to the extent that accurate readings could no longer be made.

In order to determine whether or not the effects of lightening anesthesia were reversible, the animals were re-anesthetized with ether or chloroform. An attempt was made to start the re-administration of these volatile anesthetics before the spontaneous movements of the animals had become so vigorous as to require removal and replacement of the electrodes. This was accomplished in the majority of the cases.

Ether or chloroform was administered continuously until respiration failed and the record of voltage changes in the nervous system was continued for several hours after death. By this time the dif-

ferences in voltage between any two parts of the nervous system had been reduced to less than one millivolt. The surface of the nervous system against which the electrode tips had been placed was then carefully examined for any signs of injury or damage and the experiment was terminated.

Continuous recordings were made with the aid of a General Electric Photoelectric Recorder. The abscissae on the ink-writer paper represent the time scale, and the ordinates represent the voltage. The unit lines on the abscissae are timed so that they represent an interval of five minutes. The smallest division on the ordinate scale represents a voltage of one millivolt. The base line is represented in the figures reproduced in the text by the symbol for zero. If the ink-writer is displaced above this point the electrode attached to grid is positive, and if the writer is displaced below, the grid electrode is negative. The electrodes were always placed so that the more cranial of the two sites on the nervous system was in contact with the grid electrode, although the validity of the measurement was always checked at the beginning of the experiment by reversing the position of the electrodes. The areas adjacent to the site of the electrodes were covered with dry cotton and any excessive fluid accumulation on the site was further prevented by frequent siphonings accomplished with gentle suction from a medicine dropper. The base line on the Recorder paper was checked at frequent intervals throughout the experiments, the electrodes were checked for balance, and the set was checked for balance before and after each experiment.

Records were obtained in this series for 20 rats (17 males and 3 females). The results were the same in all cases whether the animals were anesthetized with sodium amytal, nembutal, or a combination of either with ether. Sixteen recordings were made of the voltage gradient between the surface of the right or left hemisphere and the dorsum of the thoracic or lumbar cord. Four records were taken of the voltage drop between the two hemispheres. No constant differences in voltage of more than one millivolt were obtained between the two hemispheres so that the four records obtained in this way are considered negative for the purposes of these experiments. In the 16 records of the voltage difference between the cerebral hemispheres and the spinal cord reproducible results were obtained which are somewhat analogous to those of Burge. In all cases the cortex was found to be electropositive to the spinal cord. This positivity ranged between 10 and 15 millivolts in deeply

anesthetized preparations. As the animal became more lightly anesthetized, the difference in potential became smaller. Contrary to Burge, the voltage was never reduced to zero nor was the polarity ever reversed, even if the animal was allowed to come out of anesthesia to the point where its reactions were so vigorous as to preclude accurate measurements. If animals in light anesthesia or those which had recovered from narcosis were re-anesthetized with ether or chloroform, the voltage gradient again increased. The changes in the curve which followed respiratory failure are characteristic and interesting. If the curves obtained after death from ether are compared, it will be seen that they are similar (Fig. 1). If, however, an ether death curve is compared with one obtained following death by chloroform, it will be seen that they differ (Fig. 2). The ether curves are characterized by a slow rise in voltage which smoothly levels off to a maximum following respiratory failure. Several minutes thereafter the voltage drops quickly almost to the base line (it may occasionally overshoot), and then gradually levels off. The increase in voltage under the administration of chloroform, on the other hand, is steep. Cessation of breathing is quickly followed by a leveling off of the curve and this goes over into a rapid decline in voltage which is just as precipitous as the drop with ether. The fall is proportionately less, however, and the voltage then undergoes a slow, smooth rise and fall. The voltage gradients between the brain and cord are gradu-

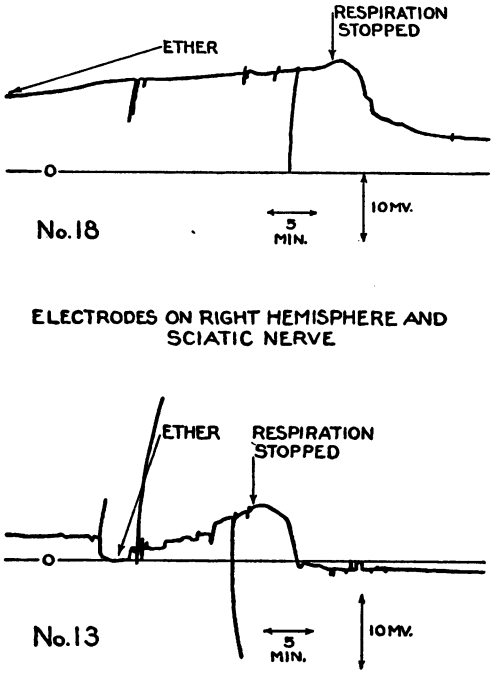

FIG. 1. Similarity between changes in the voltage gradient between brain and sciatic, and brain and cord. Administration of ether increases positivity of brain, and respiratory failure is followed by characteristic fluctuation in voltage. Sharp vertical lines are artifacts.

ally abolished within a few hours after death from chloroform or ether. No explanation of these curves is offered, but they are presented here because they are so characteristic and reproducible. It is easily possible for one acquainted with the curves to distinguish whether death was induced by either of these lethal agents. In cases where the animals died before recovering from the original anesthetic (a barbiturate) no such changes were noted. The voltage gradient slowly and smoothly falls to zero within a few hours. Three controls wherein records were taken with electrodes inserted into incisions in the head and lumbar regions were made on animals recovering from anesthesia. One of these is reproduced in Figure 3. The top record in this figure shows the characteristic drop in voltage between the hemisphere and cord in an animal recovering from anesthesia, whereas the control (lower) figure shows relatively no change. In addition, two more controls were run in which the electrodes were placed on the unbroken skin over the region of the brain and thoracic cord. These showed no changes with anesthesia. This agrees with the findings of Burr and Smith,[5] who found no relation between body voltages and the action of various anesthetic drugs.

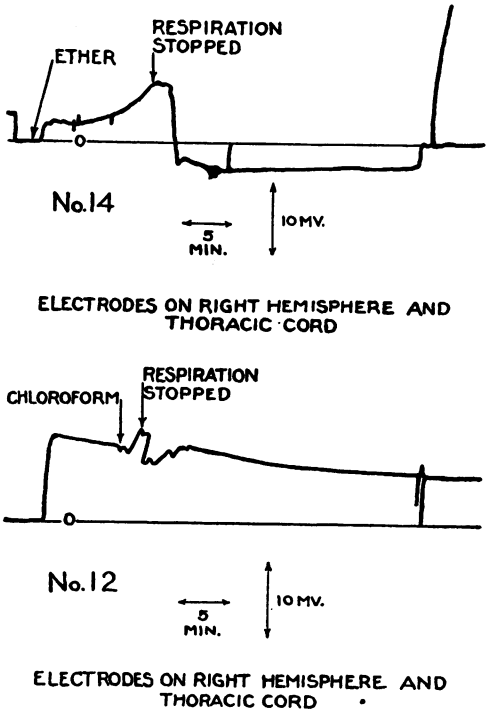

FIG. 2. Difference between changes in brain-cord voltage gradient following lethal administration of ether and chloroform. Sharp vertical line in upper graph is artifact.

Series II: Changes between the central nervous system and peripheral nerve

The instrumental arrangement and procedure were precisely the same as described above for Series I, with the exception of the place-

ment of electrodes. The electrode attached to grid in these experiments was placed either against the exposed hemisphere or the exposed thoracic cord, whereas the electrode attached to ground was placed against the exposed sciatic nerve. The hemisphere and cord were exposed in the manner described above, while the sciatic was exposed in the following way.

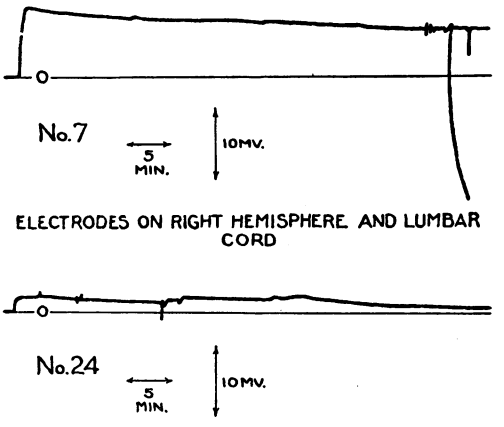

FIG. 3. Comparison of changes in voltage gradient of rats recovering from anesthesia. The gradient between the brain and cord (above) shows the lessening of the brain's positivity, whereas the control (below) shows relatively no change. Sharp vertical line in upper graph is artifact.

An incision was made with a sharp scalpel through the shaved skin on the lateral surface of the flank. The muscle mass overlying the sciatic was cleared of fascia and incised. The cut ends of the muscle were widely reflected with the aid of weighted hooks. The sciatic was then cleared of surrounding fascia (a very loose connective tissue) so that the position of the nerve which runs in the flank lay completely exposed. In the rat it is possible to clear away the surrounding connective tissues so that the middle third of the sciatic in the thigh is in no contact with the adjacent tissues. This free portion of the nerve was used as the site of placement of the electrode attached to ground. The electrodes were placed in the same manner as described above (by micro-manipulation) and the experiments were carried out as described in Series I.

Records were obtained on 12 animals (9 males and 3 females); ten of the voltage gradients between the thoracic cord and the sciatic nerve, and two between a cerebral hemisphere and the sciatic nerve. Both of the records on the hemisphere-sciatic relationship were similar to those obtained on the hemisphere-spinal cord preparation described above. One of these is reproduced in Figure 4. Voltage gradients between the cord and sciatic nerve range from 3 to 6 millivolts and apparently bear no direct relationship to the degree of

anesthesia. Furthermore, they show no consistent polarity in different rats. In five of the cases observed the thoracic cord was electropositive to the sciatic, while in the other five the polarity was the reverse.

The above results indicate that the changes in voltage with degrees of anesthesia are largely cerebral, since in no case did the voltage-drop between the brain and either the cord or sciatic nerve fail to show the characteristic changes (cf. Figures 1 and 4). On the other hand, no significant changes between the cord and sciatic nerve were recorded. It is well to emphasize that in these studies the primary concern has been with changes in voltage gradients between two parts of the nervous system. The magnitude and polarity of the gradients themselves may also be considered. On the basis of the records obtained in the above experiments, one would expect a gradient of from 5 to 7 millivolts between the brain and spinal cord of the unanesthetized rat (the brain positive). The voltage gradient between the brain and sciatic is apparently of the same order of magnitude, and the brain is also positive in this case. Gradients of the magnitude of several millivolts have also been noted between the cord and sciatic, but as stated above no constant polarity was observed in different preparations.

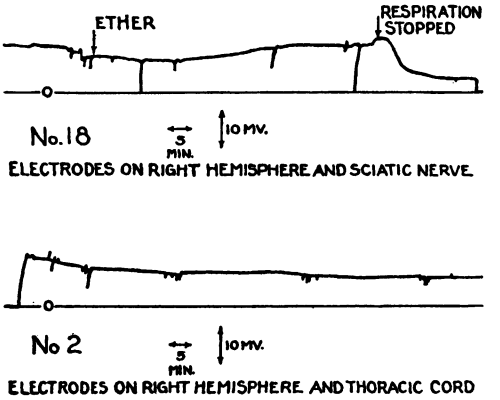

FIG. 4. Comparison of changes in voltage gradient of rats recovering from anesthesia. The decrease in brain positivity in the brain-sciatic gradient (above) is reversed by the administration of ether. The brain-cord gradient (below) continues to fall as no further anesthetic is administered. Sharp vertical lines are artifacts.

Discussion

It is now an accepted fact that biological activity is associated with electrical phenomena. It is also certain that alterations of activity may be correlated with modifications of the electrical field of living organisms. The present discussion deals with a definite kind of modification, i.e., narcosis, so that it is not strange that we find that the pertinent literature as well as our own observations show a relationship between the level of anesthesia and the electrical

properties of the system. Most of the literature on this subject pertains to the study of relatively simple systems, such as peripheral nerve (Gerard[7]) and *Nitella* (Osterhout[11]). In such simple conducting systems it appears evident that (a) anesthesia of a segment of the conducting system gives rise to a fall in the E.M.F. between that point and an intact portion, and (b) that this "negativity" is associated with the mechanism of block occurring at the poisoned spot. In the nervous system as a whole no such simple relationships have been worked out. If we omit the recent promising studies on electroencephalography (which is now being studied from the standpoint of anesthesiology) we have little to consider in the modern literature on the question of anesthesia and the E.M.F. of the nervous system. The work of Burge and his associates has been cited above. Their results can be only partially confirmed by our researches (see above) and Burge's hypothesis of anesthesia,[2] if maintained in strict form, receives no support from our experiments. Burge believes that consciousness is associated with a relative accumulation of "negative charges" in the brain. Unconsciousness or anesthesia occurs when the brain has become "exhausted" by a relative loss of negative charges and is thus electropositive to the rest of the nervous system. The reversal in sign necessary for the support of this hypothesis has never been observed by the present author in his experiments on rats. Although Burge's most complete descriptions are based on experiments performed on dogs, he believes that his results apply equally well to rats[2] so that the disparity in results must lie in the different technical procedures employed. If Burge's hypothesis is modified to state that anesthesia means a *relative* increase in positivity, and consciousness a relative increase in negativity without the necessity of a reversal in sign between the two, then our results are in essential agreement.

Analogies between our results and those obtained by other investigators on peripheral nerve are not very promising. There is, of course, the general relationship of E.M.F. to activity, but that is an approximate biological law. The chief disparity between the results obtained on the nervous system as a whole and those observed on peripheral nerve is the matter of electrical sign. Anesthesia in peripheral nerve and in many simpler systems leads to a relative "negativity," while in the nervous system a "positivity" is observed. This refers to the part of the nervous system most profoundly affected by the drug, i.e., the brain in the case of the nervous system and the poisoned segment in the case of peripheral nerve.

Since this disparity exists the author chooses to treat the nervous system as a separate case and therefore omits further discussion of the findings of workers on what would correspond, at the most, to local anesthesia in the nervous system.

Although general anesthesia is manifestly a very complex phenomenon as far as the nervous system is concerned, there is a remarkable simplicity in the E.M.F. records one obtains during various stages of the process. This points to the existence of some general process which changes with the degree of anesthesia and which affects the voltage between the brain and the rest of the nervous system in such a way as to cause a shift toward the positive as anesthesia deepens and a shift toward negativity as anesthesia lightens. An oxidation-reduction system could do this. When oxidative reactions predominated the sign would become more positive and when reduction predominated or increased the sign would become more negative. No reversal in sign would be necessary as the end-point could be positive, and the whole reaction could take place on the positive side of the zero point. It is still an open question whether cellular oxidations and reductions have any effect on saline electrodes,[6, 8, 9] so that any mention of oxidation-reduction potentials is purposely avoided. What we suggest is that when oxidative (catabolic) processes predominate the sign becomes relatively positive at the affected area, and that this situation corresponds to narcosis if one considers the sign of the brain E.M.F. relative to the rest of the nervous system. Recovery would be associated with an increase in reduction (anabolic) reactions and these would be allied to an increase in negativity, without the necessity of any sign reversal.

This view would be considerably strengthened by a demonstration that (a) oxidations and reductions going on in cells actually affect saline electrodes and (b) such reactions are affected by anesthetics in the manner described above. Experiments are in progress which are designed to throw further light on these two propositions.

Summary and conclusions

1. A study has been made of the slowly changing voltage characteristics of the nervous system in rats.

2. The relationship of the voltage gradients between the brain and other parts of the nervous system (spinal cord and sciatic nerve) to anesthesia, consciousness, and death have been investigated.

3. The magnitude of the brain-cord or brain-sciatic E.M.F. is

related to the degree of anesthesia, rising as anesthesia deepens and falling as it lightens.

4. The brain is electropositive, in the external circuit, to both the cord and sciatic nerve regardless of the degree of anesthesia.

5. The gradient between the cord and sciatic nerve is of variable polarity in different rats, relatively small in magnitude, and impervious to the level of anesthesia.

6. The voltage gradients between the brain and other parts of the nervous system undergo characteristic changes following the lethal administration of chloroform or ether and the death curves obtained are typical of the type of lethal agent used.

7. The E.M.F.'s between different parts of the nervous system disappear within a few hours after death.

8. The changes in voltage associated with anesthesia appear to be localized in the cerebrum.

9. A suggestion is made that alterations in the ratio of oxidations and reductions in the affected neurones may underlie the changes in E.M.F. noted above.

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