THE PRODUCTION OF BRAIN LESIONS WITH ELECTRIC CURRENTS
II. BIDIRECTIONAL CURRENTS

VERNON ROWLAND, M.D., W. J. MACINTYRE, PH.D., AND T. G. BIDDER, M.D.
Division of Psychiatry, Department of Medicine, Western Reserve University, Cleveland, Ohio
(Received for publication June 16, 1958)

The use of electric currents to stimulate or destroy areas of the central nervous system is a basic tool of neurophysiology and is coming into more extensive application in neurosurgery. For such use it is necessary to determine (1) the electric variables involved in thresholds of stimulation and (2) the parameters involved in histologically demonstrable alteration in brain tissue. Little investigation has been done in either case to evaluate the role in injury or to elucidate the mechanism of such destruction. The present interest in long-term and high-current applications increases the importance of quantifying electric variables critical in the production of lesions. Especially is this so in the use of long-term electrode implantations in humans, when histologic evaluation is usually unavailable and when it is important to avoid, or accurately control, the extent of tissue destruction.

Currents applied through penetrating electrodes have been quantitatively surveyed in the case of both pulsed and continuous unidirectional currents. Provided the millicoulombs (mcoul.) delivered are constant, wide variations in the time of application of the current, pulse form, amperage, and voltage do not influence the volume of tissue alteration. Furthermore, such change is found independent of transfer of heat (milliwatt-seconds or calories).

In the above studies, a partially biphasic, rectangular pulse was seen to produce considerably smaller lesions than those resulting from a net flow of unidirectional current. This raised the following questions: first, what is the relationship between the size of lesions produced by a given number of mcoul. when this charge is passed through an electrode unidirectionally as compared with bidirectionally? Secondly, does this difference derive from a lessening of the electrode-tissue interface toxicity or a reversibility caused by a restoring electric field of opposite polarity?

Since unidirectional rectangular pulses produce the same degree of injury as a similar net flow of direct current, the effect of bidirectionality can be measured by following each pulse with a pulse of the opposite polarity but

* Aided by Grant 347-C from the National Institute for Neurological Diseases and Blindness, U. S. Public Health Service.
of varying size. Any decrease in size of the lesion (i.e. protection) would then be related to some reversible process. Further differentiation between the effects of these two modes of application could be made by delivering this same charge, first by one electrode carrying current of both polarities, and secondly by using a double electrode with one wire for each. If the electrodes of such a pair were placed within 1 mm. of each other, the surrounding tissue would be exposed to virtually identical applied fields. Any histologic variation between single- and double-wire flow would thus be caused by modification in electrode tissue reactions rather than by field effects.

To investigate these properties of bidirectional currents, a systematic survey was made of the effects of pulse form, pulse dimension and mode of application on their respective lesion-producing proclivities.

METHOD

Adult mongrel cats were anesthetized with sodium pentobarbital (0.032 gm./kg., intraperitoneally). The animals were placed in a stereotaxic frame and the calvarium and dura mater were removed to expose the cerebral cortex. Except for the area through which the electrode was inserted, the surface of the brain was kept covered with gauze moistened with saline.

The majority of electrodes were prepared from 32-gauge enamelled copper wire with the insulation removed from the terminal 3 mm. of the electrode. The tip was inserted to a depth of 4 mm. into the cortex with the aid of a nonpenetrating needle stock guide held in a Johnson stereotaxic apparatus. Silver electrodes were prepared from 30-gauge Diamel-coated wire, and stainless steel from 30-gauge enamelled type 316 wire (Driver-Harris).

Unless otherwise indicated, a fresh copper electrode was used for each lesion. For less reactive electrodes, such as stainless steel, the same electrode was used throughout. As a source of rectangular and exponentially decrementing pulses, a Tektronix pulse generator was used for varying pulse width and interval independent of frequency. For sine waves, a Hewlett-Packard oscillator with minimum frequency of 5 c./sec. was used. Long-duration pulses below a frequency of 5 c./sec. were produced by switching two DC sources of opposite polarity. All currents were monitored by oscilloscope.

One hour after completion of the experiment, the animal was killed by cutting the carotid artery. The brain was removed and fixed in 10 per cent formalin for 3 to 6 days. Horizontal sections were prepared from paraffin-imbedded blocks of tissue. Weil and Nissl stains were done routinely. Selected sections were stained for copper by means of rubeanic acid. Optimal visualization of tissue copper was realized when the block of brain tissue was immediately placed in a solution of 0.1 per cent rubeanic acid in 70 per cent ethanol. After fixation for 24–48 hours in this solution, the block was put through the alcohol-fixation steps described in the reference cited above.

All measurements were made at 30× magnification for comparison. Lesions were examined at several levels to assure that a representative diameter was obtained for each. Illustrations of lesions were made by placing Weil-stained tissue sections directly in a photographic enlarger and projecting on standard enlarging paper. The black and white relations of these reproductions are, therefore, the reverse of the usual Weil preparation.
RESULTS

The transition from unidirectional to bidirectional currents was investigated by comparing the action of unidirectional current with bidirectional currents having a slow rate of alternation. Fig. 1 shows the morphologic changes arising in this comparison. The bidirectional current lesions were produced by switching the polarity of an applied direct current every 5 seconds to form a 5-second square wave pulse having a cyclic rate of 1 c./10 sec. (0.1 c./sec.). In comparison with the anodal unidirectional lesions there is an increase in central cavitation attributable to the relatively extensive formation of gas during the cathodal phase of the bidirectional current. The characteristic ring structure of the anodal lesions disappears and the overall diameter of the cross-section of the lesion is slightly reduced. The number of mCoul. indicated in Fig. 1 refers to the total accumulated mCoul. in the anodal pulses of the bidirectional current and does not include the charge contributed by the cathodal phase. If one considers the charge accumulated in both phases, the mCoul. values would be double those indicated for the bidirectional pulses. This would emphasize the reduction in size of the lesion occurring with the application of bidirectional current in comparison with unidirectional.

If the rate of alternation of the bidirectional current is now increased fifty-fold, one sees further reduction in the extent of tissue injury (Fig. 2). This reduction continues progressively until, at frequencies of about 20 c./sec. and above, production of significant lesions ceases. There is essentially

![Fig. 1. Comparison of effects of direct (anodal) and slow alternating current. Designated milli-coulombs in case of bidirectional current apply only to anodal component. The linear-scale indicator of 1 mm., shown here, is the same for all subsequent illustrations.](image-url)
no tissue damage, extending beyond the track of the electrode itself, in applications from 15 c./sec. to 10,000 c./sec. The right half of Fig. 2 shows a more detailed examination of the frequency range from 6 to 30 cycles, illustrating virtually complete protective effect occurring in the frequency range of 15 c./sec. and above. Here again the mcoul. values are those of the anodal component of the train only.

Several studies were done to investigate the relative importance of each variable, taken independently, involved in this protection with increasing frequency of alternation. The first variable considered is the time interval between the positive and negative phases of the bidirectional pulse-pair. Fig.

![Image](image_url)

**Fig. 2.** Relation between frequency and size of lesion at constant amperage. Right panel shows more detailed study in region in which effect of producing lesions disappears. The results seen with frequencies above 20 c./sec. are identical with those produced by mere placement of electrode without passage of current.

3 shows constancy of size of the lesion for a given mcoul. value, despite a 50 msec. delay between the two phases as compared with zero delay, i.e. immediate reversal. This interval has been increased up to 150 msec. with identical results.

The influence of variable pulse form was investigated from the standpoint of comparing square waves, sine waves, and exponentially decrementing wave forms in which other variables were constant. No significant variation in size of lesion could be observed with various types of wave form (Fig. 4). Note that the series of lesions made at 4 mAmp. (200 μcoul. per pulse) is larger than that made at 1 mAmp. (50 μcoul. per pulse).

Since the size of the lesion was found independent of both wave form and
delay in reversal, the degree of dependence on the amount of charge in a single pulse was next studied. Fig. 5 demonstrates constancy in size of the lesion, despite increasing frequency, if the charge in the pulse is kept constant by increasing amperage to compensate for decreasing duration of pulse. This constancy in size of the lesion is demonstrated in approximately the same frequency range as that in the right side of Fig. 2. In the latter there is a

Fig. 3. Comparison of immediate and delayed application of cathodal phase following an equivalent anodal pulse, at differing accumulated mcoul. levels. Note equivalence of size of lesion at the various mcoul. levels irrespective of immediate or delayed reversal.

Fig. 4. Lack of effect of pulse form on size of lesion as demonstrated at two values of μcoul. per pulse determined by the two amperage levels indicated. Morphological variations are more likely to appear with higher amperage as shown on the right because of increased cavitation, but volume of tissue affected is relatively constant. A further example is shown here of the independence of size of lesion from reversal delay (as shown in Fig. 3) for a value of 150 msec. by comparing the top two lesions with the bottom two.
Fig. 5. Constant size of lesion with constant $\mu$Coul. per pulse despite variations in frequency and amperage. Morphological differences appear attributable to variations in disruptive effect of gas release but do not affect the over-all size of lesion.

Fig. 6. Direct dependence of size of lesion on $\mu$Coul. per pulse. Pulse durations range from 10 to 80 msec. with 5 mAmp. peak current used throughout.
definite diminution in size of the lesion with increasing frequency simply because amperage is held constant, causing a decreasing charge per pulse.

A direct demonstration of the dependence of the size of the lesion on the charge per pulse is shown in Fig. 6, in which there is a progressive increase in size of the lesion with the charge expressed as microcoulombs per pulse.

The effects of bidirectional current, in which the charge in the cathodal phase was only 20 per cent of that in the preceding anodal phase, were compared with those occurring when the two phases were equal (Fig. 7). The protective action of the bidirectional current is found dependent on equality of charge in the two phases and rests on avoiding a net flow such as is produced by an inequality of charge.

The size of the lesion is determined not only by the charge in each pulse, but also by the number of pulses applied in a train. Trains of variable duration (variable accumulated mcoul.) were applied with each pulse in the train having a charge of 400 μcoul. Fig. 8 shows the proportionality between size of lesion and total accumulated mcoul.

The relationship between μcoul. per pulse, accumulated mcoul. in the train of pulses, and size of lesion are shown in Fig. 9 which summarizes the

![Fig. 7. Comparison of partial (20 per cent) with full charge reversal for pulses of 200 and 40 μcoul. at various accumulated mcoul. levels. Note failure to protect with incomplete reversal of charge; also, the predominant characteristics of anodal morphology with incomplete reversal and the reduction in size of lesion with increase in cathodal component.](image-url)
data for 82 lesions done in 11 cats. Beginning at 20–25 μcoul. per pulse, demonstrable lesion develops proportional to the amount of charge in the pulse and to the total accumulated charge in the pulse train. Size of lesion shows an over-all standard deviation of 40 per cent in the range of 25–400 μcoul. per pulse. This deviation is partly caused by the variability in the extent of gas production and the resultant central cavitation occurring during the cathodal phase. The extent of this deviation is considered within reasonable limits since it corresponds to a variation in diameter of lesion in the order of magnitude of ±20 per cent.

If the charge per pulse is maintained below the level of 20 μcoul., long trains accumulating up to 10,000 μcoul. may be applied without producing evidence of tissue injury, irrespective of the type of metal used in the electrode. Fig. 10 demonstrates this for silver electrodes, using 20 mAmp. peak-to-peak currents. The frequencies were chosen to assure that the charge per pulse was kept below 20 μcoul. If one proceeds to larger currents, thermal effects be-

![Fig. 8. Variations of size of lesion with total accumulated μcoul. when charge per pulse is held constant (400 μcoul. per pulse).](image)
come significant and produce readily identifiable differences in morphology of the lesion. While this effect was not studied critically, it was appreciated that thermal effects appear at much lower currents with stainless steel electrodes than with silver or copper, and may thus depend on the specific electrical resistivity of the electrode metal.

With elucidation of the electric variables primarily responsible for injury occurring with bidirectional currents, the problem of the mechanism of tissue destruction was next studied. By using two closely approximated electrodes in the brain substance and referring each of these to a third electrode placed in the paravertebral muscles of the neck, we could pass all anodal pulses through one of the electrode pair and all cathodal pulses through the other. With respect to the tissue surrounding the electrodes, the alternation of field effects produced by the two-wire system is essentially equivalent to that resulting when a bidirectional current is passed through a single electrode. Fig. 11 compares lesions made using such double-wire placements with corresponding single-wire placements and permits evaluation of the degree to which field effects are important in tissue injury. The lesions from the double-wire placements consist of contiguous, typical unidirectional cathodal and anodal lesions without any histologic evidence of protection against injury or other interaction between the lesions. If identical pulses are placed through a single wire, as shown in the middle panel of Fig. 11, there is the expected pronounced degree of protection. If both the pulses in the double-wire system are applied simultaneously, as shown in the right-hand panel of Fig. 11, there is still no protective effect as could be expected if interaction of fields were occurring.

Further observations relevant to the mechanism of lesion-formation are demonstrated in the last two figures. On withdrawal from brain, a copper electrode which has been used to make an anodal lesion is discolored because of adherent products. If, without being cleaned, the electrode is placed in a fresh area of brain tissue for a few minutes, during which it is disconnected from the source of current, a lesion is produced that is morphologically similar to the typical anodal lesion (Fig. 12). We have come to refer to this as a
Fig. 11. Comparison of identical pulses applied through single and double electrodes demonstrating development of lesion being independent of applied field.

Fig. 12. Passive-transfer effects and their neutralization. See text for details.
“passive-transfer effect.” Serial placements of this sort show decrement in size of lesion occurring with successive placements of this type. If an electrode, immediately after being used to make an anodal lesion, is subsequently repositioned in another location and used as a cathode to pass an equivalent number of mCoul., the passive-transfer effect is markedly reduced.

The absence of copper from lesions produced by bidirectional currents is illustrated in Fig. 13. Although the number of mCoul. per pulse utilized is sufficient for producing definite lesions as shown in the Weil-stained section, no deposition of copper is observed, in striking contrast to that seen in the adjacent unidirectional current lesions.

DISCUSSION

A. Factors Determining Size of Lesion. For a given number of coulombs, the extent of injury produced by a unidirectional current is appreciably greater than that occurring with a bidirectional current consisting of symmetrical pulse pairs. Therefore, it is not surprising that the slower rates of alternation would show larger lesions than the higher frequencies. Our investigation has demonstrated, however, that this increase in tissue injury is not caused by the lower frequency itself but rather by the concomitant increase in mCoul. per pulse. The size of lesions produced by these bidirectional pulse pairs is totally independent of frequency of application, wave form, and the period of time between the application of anodal and cathodal...
pulses. Two factors alone show correlation with the size of the lesion: the number of \( \mu \text{coul.} \) per pulse and the total number of coulombs accumulated in the entire train.

The decrease in size with a smaller number of \( \mu \text{coul.} \) per pulse is not a simple linear progression but shows a sharply changing slope that has permitted the demonstration of a specific coulomb-per-pulse threshold. Pulse pairs applied at less than 20–25 \( \mu \text{coul.} \) per pulse exhibit, on gross histological observation, damage no greater than that caused by insertion of electrode alone. With pulses greater than 25 \( \mu \text{coul.} \), a sharply increasing volume index of the lesion is seen which appears to reach a plateau at approximately 300–400 \( \mu \text{coul.} \) per pulse.

With values exceeding 25 \( \mu \text{coul.} \) per pulse, additional dependence of size of lesion upon total mcoul. applied in the train is found. Since the total mcoul. passing in a train is determined by multiplying the number of mcoul. per pulse by the total number of times the pulse appears in the train, each \( \mu \text{coul.} \) per pulse above 25 produces an increment of destruction which is additive.

As was found with unidirectional currents, the size of lesions produced by bidirectional charge cumulation is found to be independent of time of application, voltage applied, wave form, current, or total heat dissipated. In regard to the latter, distinction should be made between total heat dissipated and rise in local temperature. In the present study, parameters were selected to avoid currents that would cause a rise in temperature at the electrode-tissue interface sufficient to cause thermal injury of the tissue. That this selection is valid is confirmed by the absence of variation in size of lesion with 100-fold variation in the total number of calories evolved by the various pulse trains.

**B. Morphology of Lesion.** Because of the addition of the cathodal component, lesions produced by the application of bidirectional pulses show a considerably different morphology from anodal, unidirectionally produced lesions. This cathodal effect is manifested by irregular cavitation in the tissue, presumably caused by the release of gas at the electrode. This irregularity, however, is less than that seen with unidirectional cathodal lesions. Of greater interest, and in still further contrast to unidirectional anodal lesions, is the observation that no particular dependence of size of lesion on type of metallic electrode has been observed. Thus, the cathodal contribution appears dependent on the extent of gas formation and not on the type of electrode used.

**C. Interpretation of Reduction of Size of Lesion withBidirectional Currents.** The extent of injury seen with the application of bidirectional pulses may be ascribed to two general mechanisms. The first implies that damage of tissue components caused by the passage of current in one direction could be restored by passage of an equal amount of charge in the opposite direction. Such action would be similar to reversing the electrophoretic migration of a tissue component. The second possible mechanism involves a lessening
of toxic products formed at the electrode-tissue interface. For example, toxic products developed during the anodal phase may be neutralized by products, including the charges, developed during the cathodal phase. From results obtained in this study, three factors point to the protective action of the bidirectional currents occurring predominantly by means of the second mechanism:

1. **Absence of Field Effects.** Fig. 11 shows a striking reduction in size of lesion when pulses of opposite phase are carried by a single wire as compared with application through two wires that separate them, i.e., one wire carrying only cathodal and the other only anodal pulses. Since the two wires are closely approximated, the tissue surrounding them is subject to the same action of reversing electric fields as in the case of the single electrode. Thus, if it were possible to reduce tissue damage by simple reversal of the field, the double electrode should be as protective as the single.

2. **Absence of Delay Effect.** If a cancellation or reversal of tissue damage were accomplished by reversing the current, it would be expected that some time-dependence could be observed. Thus, immediate reversal of polarity could be expected to provide greater protection than that occurring with delayed reversal when time for tissue interaction with a destructive product is available. This is definitely not the case, since no greater protection is observed for pulses reversed immediately than for reversal delayed up to 150 msec.

3. **Reduction in Formation of Toxic Products.** While the exact role of the metallic ion in production of lesions is yet to be ascertained, it is observed that the size of the lesion produced by unidirectional currents is directly proportional to the amount of metal deposited in the lesion. With bidirectional currents, the striking decrease in size of lesion has been paralleled by an absence of metal dissociated from the electrode and deposited in the tissue (Fig. 13). Because of this, variations in size of lesions with differing electrode materials are minimized. This action of electrode-product reversal is further confirmed by the passive transfer effect being decreased by passing an equal current through the electrode in the opposite direction before reinsertion into the tissue (Fig. 12).

D. **Relation to Physiologic Stimulation.** The only reporting of physiologic thresholds in terms of μcoul. per pulse is that of Lilly and associates,\(^7\) who found stable thresholds at a value of 0.2 μcoul. per pulse on monkey cortex. Other physiologic responses (e.g., purely electrical events) probably exist at lower threshold values. Therefore, the difference between physiologic threshold (0.2 μcoul. per pulse or less) and injury threshold (20–25 μcoul. per pulse) is at least a factor of 100. In the present investigation, low-power magnification has been used throughout. Detailed microscopic studies of the various types of lesions are in progress and may indicate the need for a slight downward revision of the threshold value of injury. Of interest, however, is the fact that within the limits of observable histologic injury, total cumulation of 10 coul. (bidirectional pulses) has been applied with no
destruction other than the minimal amount occurring with insertion of elec-
trode. It must be emphasized that the absence of gross histologic damage
cannot be taken as evidence for the absence of injurious physiologic effect.

The present studies were done on acute preparations, and application to
chronic implantations requires further study. If no further changes occur
with more prolonged application of currents, these data imply that bidirec-
tional pulse pairs of 0.2 $\mu$Coul. per pulse, at a rate of 60 pulses per sec., could
be applied continuously through a nonreactive electrode metal such as stain-
less steel for over 200 hours (total accumulated charge = 8.6 coul.) without
noticeable histologic effect.

**SUMMARY**

The effects of bidirectional electric currents in producing lesions in cat
brain have been studied and compared with those resulting from the applica-
tion of unidirectional currents.

The size of lesions from bidirectional currents are dependent on (1) the
number of $\mu$Coul. per pulse in excess of a threshold value determined at 20–25
$\mu$Coul., and (2) the number of such pulses in the applied train.

Such lesions are found independent of the frequency, pulse duration,
pulse height (amperage) and voltage, when studied as independent variables.
They are also independent of the wave form, the time interval between
anodal and cathodal phases of each pulse pair and the type of metal in the
electrode.

Bidirectional pulses containing fewer than 20 $\mu$Coul. may be applied in
trains cumulating 10 coul. or more without evidence of tissue alteration.
Above 25 $\mu$Coul. per pulse a sharply increasing index of the volume of the
lesion is seen which appears to plateau at approximately 300–400 $\mu$Coul. per
pulse.

Lesions from bidirectional current, compared with those from unidirec-
tional current, show marked reduction in size. Morphologically, they appear
as a combination of the individual cathodal and anodal effects with one
major difference—the absence of electrode metal in the lesion.

Absence of field effect, absence of change in lesion with variable delay
between cathodal and anodal pulses, and reduction in metal deposition with
bidirectional currents point to the interpretation of the protective actions
of such currents being one of reducing the formation of toxic products rather
than simple reversal of electrophoretic displacements.

A factor of at least 100 has been estimated between the threshold of
histologic damage shown here and the threshold of physiologic stimulation.

The authors wish to express their thanks to Miss Kate Gruen for her collabora-
tion in preparation of histological sections.

**REFERENCES**

BRAIN LESIONS PRODUCED BY ELECTRIC CURRENTS


