64. Lilly, John C. 1961. "Injury and Excitation by Electric Currents." Chapter 6 in Electrical Stimulation of the Brain. Daniel E. Sheer, Ed., Univ. of Texas Press for Hogg Foundation for Mental Health, Austin, Texas. P. 60-64

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Reprinted from Electrical Stimulation of the Brain, 1961
Printed in United States of America

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CHAPTER 6

Injury and Excitation by Electric Currents

A. *The Balanced Pulse-Pair Waveform*

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OUR GOAL HAS BEEN to find an electric current waveform with which animals could be stimulated through implanted electrodes for several hours per day for several months without causing irreversible changes in threshold by the passage of current through the tissue. We have found one such waveform (Lilly *et al.*, 1955*a, b, c*), shown in Fig. 6.1. There are certain ultimate limitations in the use of any electrical waveforms, including the one illustrated here. The search for an ideal waveform is being continued; the ideal one is only approached, not achieved, by the waveform of Fig. 6.1.

The present chapter treats of the thermal energy limit and the electrolytic limit which are reached as the neuronal threshold data are traced through large systematic changes of waveform. However, the discussion concerns only chronic persistent stimulation—that is, 1 to 3 trains per second for up to 18 hours per day, 5 to 7 days per week for 6 to 12 months. It does not concern acute stimulation at one session or stimulation for one hour per day for several weeks. Many waveforms, including 60-cps. sine-wave current (Olds and Milner, 1954), can apparently be used safely for these limited schedules of stimulation. In our experience they cannot be used for the intensive, long-term schedule of chronic stimulation. (See Lilly, 1956, 1957*a* to *d*, 1958*a, b, c*, 1959*a, b*; Lilly *et al.*, 1956*a, b.*)

INJURY

Electric current passed through the brain can cause at least two distinct types of injury: thermal and electrolytic. These two types are separable by the proper choice of electrical parameters and, in the proper parametric regions, can have thresholds less than those for excitatory processes. The technical problem in chronic brain stimulation is to stay above the excitatory threshold and below the injury threshold in the neuronal system under consideration. This result can be achieved most easily by the proper choice of waveforms and their time courses; and less easily by the choice of the range of repetition frequencies and train durations (Lilly *et al.*, 1952). As has been amply demonstrated (Liddell

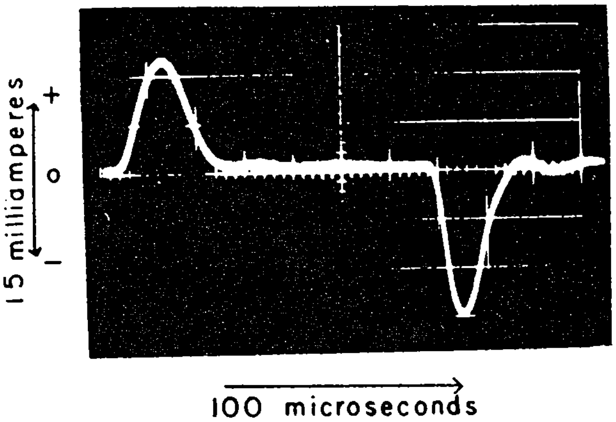

FIG. 6.1. Waveform of stimulating current: pulse pairs of current resulting from quasi-differentiation, with passive electrical elements, of a rectangular pulse. Measured at 2 per cent of the peak, the duration of the positive pulse (upward) is 34 μsec., and the duration of the negative pulse (downward) is 28 μsec. The areas under the two pulses are equal; therefore the negative coulomb flow is zero for the pulse pair algebraically summed during a time interval of 200 μsec. from the beginning of the positive pulse. (From Lilly *et al.*, 1955*a.*)

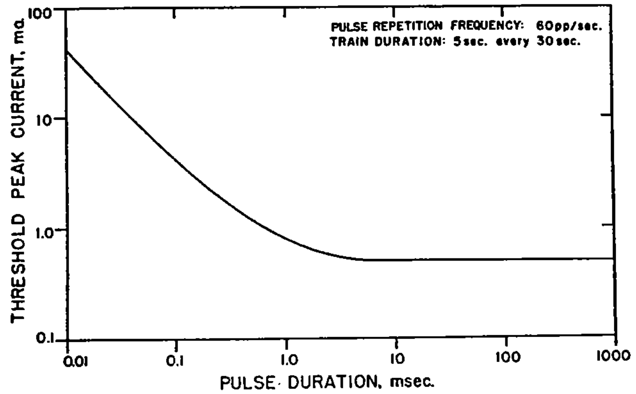

FIG. 6.2. A typical "strength duration" curve for a cortical zone using unidirectional rectangular pulses. The threshold current (at 60 pulse pairs per second, in trains 5 seconds long repeated at 30-second intervals) is shown as related to the pulse duration, on a log-log plot. Beyond about 5 msec. is the "rheobase" plateau, i.e., "constant current" threshold; such long pulses cause rapid electrolytic injury. Below 0.1 msec. is the 45° constant slope showing a first-power relation between current and pulse duration; this is the "constant quantity" region of excitation. In the very short (0.01 msec.) duration region such pulses can cause thermal injury at threshold.

and Phillips, 1951; Lilly *et al.*, 1952; Hess, 1954*c*; Cure and Rasmussen, 1954), these parameters also influence excitatory thresholds and possibly determine which systems are excited in the vicinity of the electrode.

Our first emphasis is on avoidance of injury. We proceed on the basis of accepting—as threshold excitation of any or all systems at the electrode tip—the values of current which give a visually or tactually detectable response or change of behavior. (Of course, other methods of detection can give lower threshold values, and other waveforms can excite other systems at the electrode ["preferential" excitation], but these subtleties are not germane at this point.) We are looking for those characteristics of waveforms which cause excitation but do so without injuring brain tissue after many hours or days of stimulation.

The two types of injury are possibly best illustrated by the effects of two extreme types of waveforms. Unidirectional direct current causes electrolytic injury (Horsley and Clarke, 1908) but little excitation, if increased from, and then decreased to, zero value sufficiently slowly to allow accommodation to take place in the nervous tissue. High radio-frequency currents (greater than, say, 200 kilocycles) can cause thermal injury by overheating the tissue without excitation and without electrolytic injury if no rectification is allowed to occur (in the circuit, and especially at the electrodes). Apparently the amount of electrolytic injury is related in great measure to the total quantity of unidirectional electricity (coulombs) passed through the tissue in a given interval without reversals, whereas the amount of thermal injury is more closely related to the total energy (watts) passed.

Both these types of injury can be shown to exist in some other waveforms in the intensity ranges of interest in brain stimulation. As an example, in the case of unidirectional rectangular pulses we choose the threshold for the amount of excitation of, say, cerebral cortex, to excite movement in the periphery in the unanesthetized monkey. For any given pulse duration we choose a repetition rate sufficiently high (50 to 200 per second) so that we can keep the threshold current low. As we increase the pulse duration, the current at threshold becomes lower until we reach rheobase, at about 5 msec. (Lilly *et al.*, 1952). But as we change pulse duration, the quantity of electricity passed and the energy dissipated at each threshold value are also changed. If the electrodes are nonpolarizable (Lilly *et al.*, 1952), the resistance is constant with time and with pulse duration changes; and the energy (watts) per pulse is given as peak current (amperes) squared times the resistance (ohms) of the electrode. The amount of electricity (coulombs) passed per pulse is the product of the pulse duration (seconds) times the peak current (amperes). To illustrate the points involved, some values have been calculated for a representative implanted electrode in a monkey. The results are shown in Figs. 6.2 to 6.5, in all of which pulse repetition frequency is held constant at 60 pulses per second, and train duration at 5 seconds.

Figure 6.2 shows the relation between the threshold current and the pulse duration. The classical rheobase is difficult to obtain because of the electrolytic injury, which raises the threshold rapidly; the value here is an extrapolated estimate.

Figures 6.3, 6.4, and 6.5 are calculated from the data of Fig. 6.2. Figure 6.3 gives the threshold peak energy per pulse; Fig. 6.4, the threshold quantity of electricity per pulse, each plotted against the pulse duration; and Fig. 6.5, the energy plotted against the quantity. In each of these graphs an estimate is given of the threshold for the two types of injury: thermal in Fig. 6.3; electrolytic in Fig. 6.4; both in Fig. 6.5. However, it is suspected that the electrolytic injury threshold is very much lower than this value; the lower limit is yet to be determined carefully for stimulations lasting many days. The thermal injury threshold is an estimate based on the observation of the breakdown of water (in normal saline) to steam for single pulses at a metallic electrode whose resistance was the same as the electrode used in determining the data on these graphs; the values for tissue damage are probably lower than the one estimated here. This threshold is a function of the area of metal exposed and the size and efficiency of the heat conduction path away from this electrode interface; however, the value is of the approximately correct order of magnitude for practical electrodes. As the area of the metal in contact goes down (smaller electrodes) and hence the resistance goes up, the threshold energy may reach such values that the local temperature reaches injurious levels at local threshold values of current.

We have found (Lilly *et al.*, 1955*a*) that if a 120-microsecond rectangular pulse is quasidifferentiated (to a pulse duration of about 30 μsec.) and the resulting pulse pair (Fig. 6.1) is used to stimulate, no detectable injury occurs over many weeks of stimulation. Apparently this short-term (within 200 μsec.) reversal of current, with equal charge in each of the opposite pulses, reverses processes leading to "electrolytic" injury.

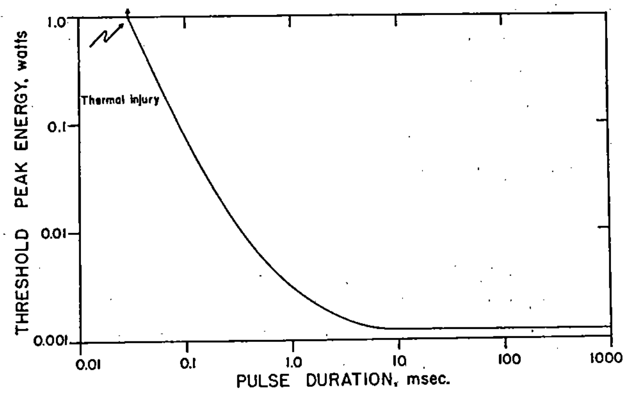

FIG. 6.3. Peak dissipated energy versus pulse duration at threshold. The data are calculated from FIG. 6.2 in this and subsequent figures. For this electrode, waveform, train duration, and train repetition rate, the thermal injury threshold is approximately 1 watt peak power at about 0.02-msec. pulse duration.

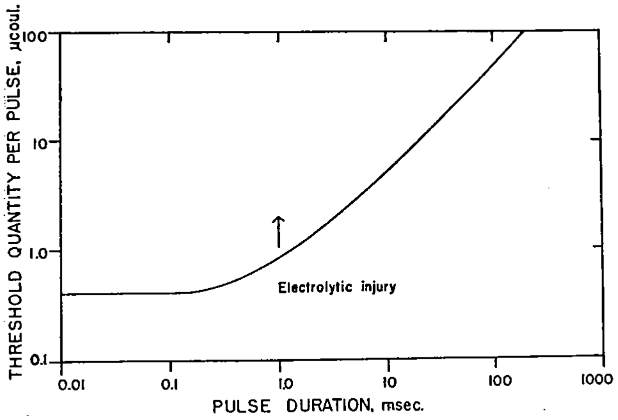

FIG. 6.4. Quantity of electricity per pulse versus pulse duration at threshold. For this electrode, waveform, and train parameters, the electrolytic injury threshold is at about 0.5 microcoulombs per pulse at about 1.0-msec. pulse duration.

In some experiments we found that if the pulse-pair interval was extended to 16 μsec. (60/sec.) and the duration of each condenser-discharge type of pulse was extended to a time constant of 5 μsec., the threshold rose slowly in the first few hours of stimulation (deep, subcortical electrode). We then changed to the short pulse pair; the threshold stayed at the final value for six months. Many experiments in several loci, at many "dosages," demonstrated that "electrolytic" injury was being generated by this longer pulse pair. In other experiments the duration of each member of the pulse pair was shortened to 10 μsec.; at threshold values of current the threshold rose rapidly until breakdown of water began to interrupt the current seen on an oscilloscope. The peak energy dissipated per pulse was of the order of 2 watts. The thermal injury level was exceeded by these very much shortened pulses. Thus for the matched opposite pulse pairs there are two extremes, limiting the range applicable to brain stimulation without injury: the lower, low current, low energy, high quantity pulse pair causing electrolytic injury; the upper, high current, high energy, minimum quantity pulse pair causing thermal injury.

In other experiments we found that even in the presence of a 100 per cent rise in threshold resulting from electrolytic injury (maintained for six weeks), the damage was not detectable under the microscope; only very much larger increases in threshold were correlated with visible damage.

EXCITATION

In general, the threshold under discussion here is for either demonstrable evoked movement or some change in what the monkey did in response

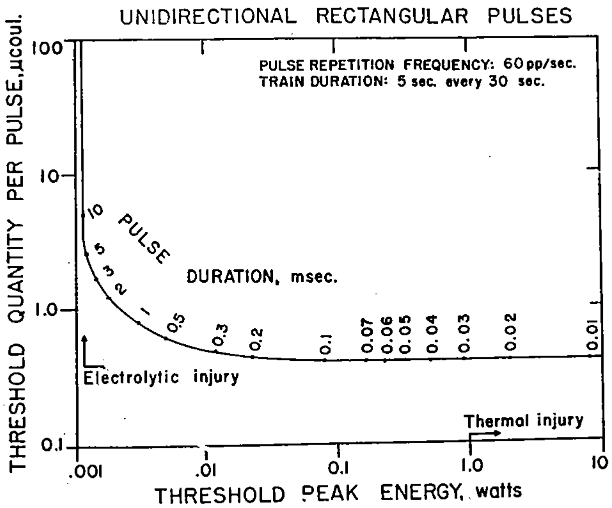

FIG. 6.5. A relatively minimal-injury parametric region: quantity versus peak energy at threshold at various pulse durations. (Data are combined from FIGS. 6.3 and 6.4.) Both of the injury thresholds for the parameters previously given are shown. The vertical straight-line portion of the curve is "rheobase" and the horizontal one is "constant quantity" on this plot. It is to be emphasized that for maximum safety the waveform of FIG. 6.1 is to be used. No region for the *unidirectional* waveform can be used longer than the times given (5 sec. every 30 seconds) without causing electrolytic injury. It is also to be emphasized that the waveform of FIG. 6.1 can be shortened or extended to give results like those in FIGS. 6.2 to 6.5. Values of the injury thresholds very close to the ones of the above illustration are found for such shortened and extended forms for very long trains applied continuously for hours per day for several weeks. The bidirectional waveform in the proper parametric region extends the permissible total stimulation time of each session by many hours.

to stimulation. The first threshold is definitely higher than for the minimum evokable local electrical activity, and the second can be of a magnitude comparable to that of the electrical response (Lilly, 1958*a*, *c*).

As can be seen from the illustration, the short pulses (and pulse pairs) have a constant quantity of electricity per pulse at threshold; these quantities are of the order of 0.2 to 0.5 microcoulombs per pulse at 60 pulses (or pulse pairs) per second in 5-second trains for pial electrodes over cortex, and about 0.05 microcoulombs for some deeper placements. The long pulses have, temporarily, a constant current threshold (rheobase of the order of 0.2 to 1.0 milliampere) but such pulses destroy tissue.

Hess (1954*c*) used a very long duration "balanced" waveform, in order to excite all elements near the electrode in equal amounts. We do not know how long he stimulated in each session (hours) nor for how many days or weeks he observed thresholds. If these times are comparable to ours, and the thresholds remained constant, the facts in the two cases disagree, and further research is needed.

The shorter balanced pulses may possibly stimulate only short chronaxie elements, but this is doubtful. To obtain an observable effect on behavior requires firing several thousands of elements near the electrode. The local field strengths near the electrode at the currents observed are presumably very much above threshold for even small fibers. Apparently the shell within which small, long-chronaxie elements fire is smaller than the shell in which the larger, short-chronaxie elements respond. With the longer pulses (resembling Hess's case), the two shells may be more coincident in space. However, it is yet to be demonstrated that these differences do not average out in the mass of excited elements, rendering them undetectable by behavioral criteria. A point-to-point comparison should be carried out, in which, if possible, injury is avoided. There may be a different injury threshold for each of the different elements, analogous to but not identical with the differences in excitation thresholds (Lilly, 1950*b*, 1952, 1954; Lilly and Cherry, 1954, 1955).

EFFECTS

The criteria for truly long-term frequent stimulation were developed in the course of a program of mapping the monkey's brain for elicitable behavioral, emotional, and motor effects of localized electrical stimulation. In some systems ("start" systems), the animals could be trained to start the stimulus trains repetitively in their own brains ("start capture," Lilly, 1958*c*; Olds and Milner, 1954); in other systems ("stop" systems), they could be trained to stop trains started by the apparatus or by the observer ("stop capture," Lilly, 1958*c*; Delgado *et al.*, 1954*b*); in still other systems ("alternating" systems), they would start a train of several seconds' duration several times and then stop such trains several times (Lilly, 1959*a*, *b*).

In the "start" systems the sessions would last up to 12 to 16 hours per day at an average train repetition rate of at least 2 trains per second and peak rates up to 18 trains per second, 7 days per week up to 18 months; each train was about 6 to 12 pulse pairs at a frequency of 60 pulse pairs per second. The number of trains delivered per day was from 80,000 to 260,000. In one spot in one monkey the total number of trains delivered over a 6-month period was approximately 15 million. The number of pulse pairs delivered was 180 million, or about 10 coulombs (0.06 microcoulomb per pulse pair).

In the "stop" systems, with the crescendo train technique, trains were started by the apparatus every 12 seconds and stopped by the animal at his own chosen threshold. Because of deleterious effects on the animal as a whole, these sessions were limited to 3 hours per day (900 trains) for several weeks (100,000 trains), or to unbroken 48-hour sessions (18,000 trains) without sleep. Each train had an average of about 300 pulse pairs at threshold. The stop system loci thus received up to 30 million pulse pairs or about 1.8 coulombs for 0.06 microcoulomb per pulse pair.

In the "alternating" systems the figures are similar to those for the "stop" systems for the same reasons. The sexual systems, at least those subsidiary to erection in the male, show the "alternating" property extremely clearly.

Careful quantitative data concerning the spatial factors in electrical excitation are conspicuously absent in the literature. Many more data and much more analysis are needed for evaluation of the results of stimulating closely packed systems like the hypothalamus, intralaminar nuclei, etc. At best, localization of function in the central nervous system suffers at present from the lack of a truly quantitative theory based on what is done in the laboratory rather than on some neuroanatomical conjectures. Obviously, the neuroanatomical findings are essential; they contain the most quantitative data we have to date. But an understanding of function requires, in addition, a biophysical quantitation of the geometry of the relations between excitation and the field set up by the current.