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1. Production and avoidance of injury to brain tissue by electrical current at threshold values. — JOHN C. LILLY, JOHN R. HUGHES, THELMA W. GALKIN and ELLSWORTH C. ALVORD, Jr., National Institutes of Health, Bethesda, Md.

In recent years, several groups of investigators have begun stimulating the brains of patients for long periods of time through electrodes implanted in deep structures. In work of this nature, it is desirable to avoid injury to the structures involved, especially damage due to electrical current. As is well known, direct currents destroy nerve tissue (Horsley and Clark 1908). Some evidence (Lilly, Austin and Chambers 1952) indicates that unidirectional rectangular pulses can also destroy nerve cells.

In order to test motor and other thresholds and their changes during and after injury, a non-injurious electrical waveform is essential. We have found one such form of electrical current (1955). This waveform consists of a brief pulse (30 μ sec.) passed through the tissue in one direction and a pulse of an equal net charge passed in the opposite direction within 0.1 msec. It was found that such a waveform applied to cerebral cortex gives motor movements very similar to those found previously with unidirectional pulses and with sine waves. By passing such a waveform through the brain of unanesthetized macaques with implanted arrays of 36 to 121 electrodes, we found no evidence of injury after 6 to 22½ weeks exposure for 4 to 5 hours per day at threshold.

Using this waveform to continually check threshold, we have recently found that passing unidirectional pulses raises this threshold in an irreversible manner. One electrode of an array was exposed to unidirectional pulses at threshold current values (1 msec. duration, 5 sec. trains, 2 per min.) for a period of 4¼ hours. We found, with the pulse-pairs, up to a 125 per cent rise in threshold for movements developing within the first 24 hours after the exposure. The gradient of threshold change across the surface of the cortex was determined by other electrodes in the array; in the first few mm. the gradient was found to vary inversely as the square root of the distance from the electrode exposed to the unidirectional pulses. Detectable rises of threshold amounting to 10 per cent could be found as far away from the exposed electrode as 10 mm. along a gyrus. This rise in threshold and gradient was found to be maintained during the next 2 weeks without significant change from the level at 24 hours after exposure.

We have evidence that this bidirectional waveform is within the constant coulomb region for stimulation of cortex. Shortening the interval between the two pulses to values less than 0.1 msec. results in a rise in threshold; lengthening the interval between the two pulses gives no change of threshold for intervals from 0.1 msec. to 5 msec. Hence, the present waveform passes the minimum number of coulombs through the tissue at threshold for excitation. Shorter pulses than these probably require total energies so high that the heating effect will begin to destroy tissue.

These results suggest that one mechanism of injury by the passage of electrical current through tissue may be the displacement of large charged particles (proteins, enzymes, etc.) from key positions in the cells over relatively long times by a process analogous to electrophoresis. These processes are slower than the excitatory ones and are presumably reversible by passing an equal charge in the opposite direction within a short period of time; the critical time interval for injury is yet to be determined.

Discussion :

Dr. OFFNER : For a number of years we have been making electroshock apparatus using the brief stimulus current proposed by Dr. Liberson, who uses a monophasic wave form of just about this form up to 1 msec pulse duration.

It seemed to me on physical-chemical grounds that a truly unidirectional current could cause injury, and so I made the apparatus to give not pulses in both directions, but rather an average of zero D.C. transfer by shifting the baseline so the pulses go up, and then there is a small reverse current in the opposite direction to equal it. I wonder if Dr. Lilly believes that this would have the same effect in eliminating injury as using pulses in opposite directions.

Although I believed it possible that this would occur, I still wonder whether the occurrence of injury in these preparations is perhaps due to the metallic electrode effect in which you get an actual electrolysis and therefore perhaps the liberation of HCl at the anode, and on the cathode you would get perhaps NaOH liberated, a breakdown of NaCl or whatever electrolyte is there.

In direct metallic contact with the dura or the brain, however it was arranged, if he had used a wick electrode so that the products of electrolytic discharge were not directly in a position where they could diffuse into the brain, I wonder if he believes, in that case, that he would obtain the same injury.

This is important, because in electroshock the electrode is on the surface of the scalp, and the electrolytes which may be found would not diffuse into the brain.

Dr. SEM-JACOBSEN: I have enjoyed this paper very much. I have one question.

Have you tested your stimulus and seen if any changes appear in the recording after the stimulation is terminated, particularly if any 1 to 2 c/sec. slow waves of medium to high voltage are found ?

We know that after stimulation with 0.5 to 1 mA and 2 V., slow waves are frequently encountered. They also appear when using the same electrodes, technique and stimulus in a jar of egg white. The same slow waves are encountered. Transient flocculation is seen at the same time around the contacts. This has nothing to do with neuronal activity.

We feel that these slow waves are a very good indicator of injury, and I would like to know your ideal stimulus rates in this test.

Dr. THOMAS: In contrast to the theoretical calculations regarding the heating effect, does Dr. Lilly have any experimental evidence, such as temperature measurement in the stimulated area?

Dr. BICKFORD: We have recently had some experiences with what might be called the parameters of an hallucination induced by depth stimulation. In an epileptic patient we were able to plot the parameters of an induced hollering noise which he said was caused by voices.

It appears to us that in confirmation of what Dr. Lilly said, the short duration pulses are not only very effectual, (although this has been doubted by others in the past), but the 0.01 msec. pulse is rather the more efficient, taking into account the lesser amount of current expended. In human stimulation work we should obviously use these very short durations in order to avoid tissue damage.

We have also had the experience of change of threshold with sleep in the case of a pyramidal tract stimulation in man, the results of which we will present a little later in this meeting. The threshold increased markedly during sleep in one patient. In another case we recently investigated with head turning, the threshold remained quite the same in waking and sleeping states, so apparently there can be both situations depending upon the system being stimulated.

Dr. LILLY (*closing*): In answer to Dr. Offner's questions, first of all we know very little about the effects of shock therapy on the brain. Secondly, we have not tested his type of waveform on the cortex, so I can't say whether it is injurious or not.

He wondered if metallic electrode electrolysis effects came into the picture. Undoubtedly they do with unidirectional pulses. As I said in the paper, within a short distance of the electrode they are probably very important. Farther away you would not expect them to be so important, because the circulation can probably handle diffusing ions at some distance away.

Concerning the question of using a nonmetallic electrode, we have published some data: we used a nonmetallic electrode and showed extensive damage for unidirectional pulses. I want to emphasize again that these are truly unidirectional. We placed a diode in the circuit to prevent the back potential from the electrode from causing current flow through the tissue.

In answer to Dr. Sem-Jacobsen, about whether we saw any slow waves, we haven't looked in time to see the transient slow waves that he sees after unidirectional pulses. We have not seen any produced by the bidirectional pulses. We looked at the electrocorticogram for the bidirectional ones, but we haven't investigated the case of the rectangular pulses.

In regard to Dr. Thomas's question of whether we measured the local temperature, no, we have not; but we have not seen any fried arachnoid or dura.

We intend trying out the bidirectional waveform on Dr. Sem-Jacobsen's "egg white" preparation to see if the heating effect is enough to cause any appreciable white precipitate to appear around the end of the electrode.

I was very much interested in Dr. Bickford's presentation. I wonder where he had been stimulating to evoke the hallucinations.

We do have one point here that I would like to emphasize, namely, that if you use pulses which are very much shorter than the ones we have shown, undoubtedly the threshold for energy dissipation and damage to tissue by heat will come into the picture. In fact, we have tried shortening them to two 10 microsecond rectangular pulses of equal coulombic value on each side of zero, first positive and then negative, and watched the electrodes under a microscope. If you make the current high enough you can see steam at the tip and a little flash of light as a spark jumps the gap in the steam cavity. Hence, in further answer to Dr. Thomas, there is an upper limit to how short you can make the pulses, and that is the total energy dissipation limit determined by how high the threshold is, current-wise, and how high the electrode impedance is.

We have several experiments bringing one of these pulses closer to the other one than the 100 μsec. value that we showed you here; if you keep the pulses at least 100 μsec. apart and then move them farther apart in time, you find that the threshold does not change at all, even as far apart as 5 to 10,000 μsec. As you get them closer together than 100 μsec., the threshold starts rising abruptly, and as they get closer and closer you may quickly get thresholds up to 10 times what it is with the interval at 100 μsec.

So, here too, one will also get into the energy dissipation limit at which you will begin to fry tissue if the pulses are brought any closer together than 100 μsec. This is also an indirect proof that the duration of our pulses is within the constant charge region for neuronic excitation; as one pulse gets closer to the other the second one begins to cancel the first, and the threshold rises.