# Local Effects of Epinephrine on the Cerebral Cortex. (20341)

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Recent work has shown(1) that small doses of epinephrine, injected intravenously or intra-arterially into the cat, prolong the duration of electrically induced seizures and shorten the period of extinction after electrical stimulation. It seemed of interest to consider the effects of locally applied epinephrine on the excitability of the cerebral cortex.

These experiments were carried out on the adult monkey (*Macacus rhesus*) under moderate Dial anesthesia (40 mg/kg). The anterior part of the hemispheres was exposed; the dura was opened and the motor arm areas located on both sides. A bipolar electrode was placed on each hemisphere with the negative pole in the arm area just anterior to the central sulcus, the positive pole, posterior. The selected areas were stimulated with a thyratron stimulator, producing condenser discharges of 1 msec. time constant at 50 impulses per second for 2 seconds. Stimulation of both areas set up equal movements in the corresponding hands. The voltage employed (around 6 volts) was just sufficient to elicit the chosen movement when there were no after-effects from previous stimulation. Cortical excitability was evaluated by recording cortical and muscular responses to a pair of stimuli, the second separated from the first by increasing intervals of time. The pairs of stimuli were applied to the hemispheres alternately 3 minutes apart. In order to discover whether changes in the cortical responses of these stimuli after local application of epinephrine accounted for the augmentation of motor responses, we recorded: 1) the electrocorticogram from the stimulating electrodes, 2) the electromyogram from the groups of muscles involved, 3) the movement.

*Results.* A) *Control curves.* The first stimulus evoked a movement in the opposite hand; the second stimulus, initially given after a very short time interval, regularly elicited cortical and muscular after-discharges. The interval between the stimuli was then progressively increased until the second stimulus failed to produce any after-effects. This interval was generally between 4 and 8 seconds. Different intervals were found for electrocorticographic, myographic and mechanical measurements of after-discharges. The first can be recorded in the absence of the others. With a slightly higher voltage, cortical after-discharges may be accompanied by a small myographic pattern characterized by rhythmic discharges of motor units. With still higher voltages, the myographic record becomes complex and movement always occurs.

B) *The effect of epinephrine.* After recording control curves of all responses and their facilitation for the series of intervals, a small piece of filter-paper soaked in epinephrine solution (1/1000) was placed on one cortical arm area. The electrodes were replaced, the positive, posterior as before, the negative, anterior, on the filter-paper. Cortical activity was then immediately recorded and the excitability tested as before by determining the responses to pairs of stimuli, alternating between treated and untreated hemispheres, at progressively increasing intervals (Fig. 1).

The epinephrine employed in 3 experiments was a product going under the trade name of "Suprarenin-Bitartrate"—Winthrop; it contained synthetic l-epinephrine bitartrate in isotonic solution, 0.5% chloretone and 0.2% sodium bisulfite. The immediate effect of this solution applied on the cortex was a considerable decrease in amplitude with disappearance of high frequencies of the corticogram from the treated area (Fig. 2). In spite of this apparent depression, stimuli applied to the treated area produced after-discharges at noticeably longer intervals than on the untreated side (Fig. 3). Finally, the first stimulus, which originally caused only the selected muscular movement, was late in the experi-

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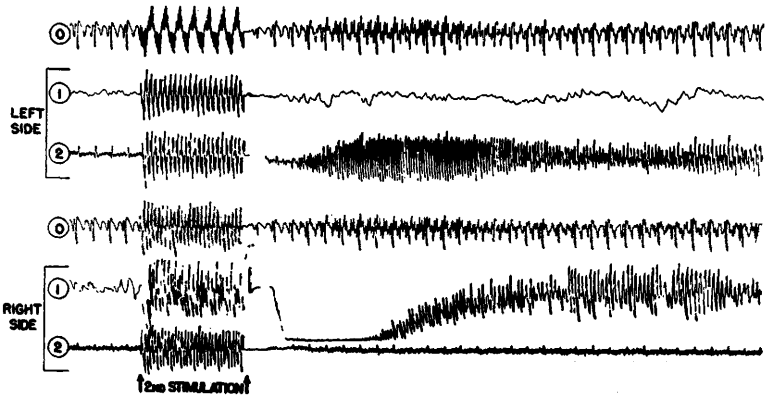


FIG. 1. Effect of a second cortical stimulation on the right side. (1 msec. 50 impulses per sec., 6 volts during 2 sec.) First stimulation, 4 sec. before, is not shown. 0—electrocardiogram; 1—corticogram of the hand motor cortex; 2—myogram of ipsilateral hand muscles. After stimulation, there follows a transitory alternation of record (1) on the right side (cortical after-discharge) and of record (2) on the left side (myographic after-discharge).

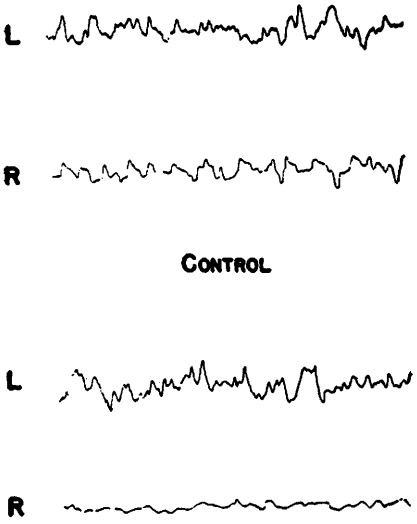


FIG. 2. Corticograms of right and left cerebral cortex before and immediately after local application of epinephrine to the right side.

ment infrequently followed by after-discharge. Occasionally, this last effect was not limited to the treated side but appeared, after a considerable delay, on the control side, in which case there was always a parallel modification of the electrocardiogram, with bradycardia and arrhythmia, suggesting passage of epinephrine into the circulation. Three other experiments performed with a freshly prepared solution of epinephrine with 1/1000 barbiturate and three experiments with a similar epinephrine solution with 1/1000 chlorhydrate instead of barbiturate failed to show the cortical depression observed in our first experiments.‡ It is thus possible that that phenomenon may be due to chloretone, though similar effects have been obtained with eserine and acetylcholine on the cat's cortex by Miller, Stavraky and Wooton(2). Local application of these epinephrine solutions elicited, however, in all our experiments the

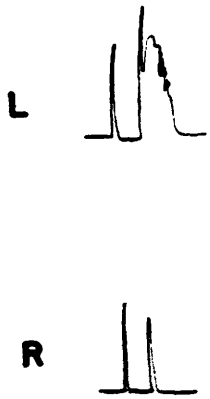


FIG. 3. Kymographic record of the same movement on both sides. On the left after application of epinephrine the movement following a right cortical stimulation is complicated by an after-discharge after the second stimulation.

‡ From previous work in this laboratory it is known that bisulfite in the concentrations employed here does not depress cortical activity.

appearance of muscular after-discharges for longer intervals than on the untreated side; we further found an increase in duration of cortical after-discharges and a decrease of about 30 percent of the voltage necessary to produce movement. This observation may be of interest in connection with McCulloch's recent findings(3) that eserine and atropine which generally sensitize and inhibit central acetylcholine effects and which have been found to prolong and to shorten respectively the period of cortical facilitation, do not produce any change in the cortical threshold to electrical stimulation.

Local application of an epinephrine solution 1/10,000 as well as that of isotonic saline, was ineffective in our control experiments.

*Conclusions.* 1. On the basis of these results, it may be concluded that epinephrine stimulates neuronal aggregates in the cerebral cortex. 2. The local effect is marked by an increase in duration and intensity of the period of over-excitation subsequent to a stimulus eliciting movement, and it is characterized by the appearance of after-discharges of cortex and muscle after stimuli just sufficient to produce movement.

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## Experimental Poliomyelitis. Studies in Mice with Human Gamma Globulin. (20342)

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Recent preliminary evaluation of gamma globulin as a prophylactic agent for poliomyelitis in children by Hammon, Coriell, Wehrle, Klimt, and Stokes(1), demonstrated significant temporary protection. Experimental study of gamma globulin to determine dosage, time of administration, and duration of passive protection, becomes a matter of considerable importance.

The data in the present report deal exclusively with studies in mice which offer a convenient though limited tool for investigating certain quantitative aspects of the problem. Bodian(2) protected cynomolgus monkeys with doses of gamma globulin as small as 0.1 ml/kg of body weight when the poliomyelitis virus was fed immediately after the administration of gamma globulin. Adams and his co-workers(3,4) found that when cynomolgus monkeys were tonsillectomized, much larger doses were required for protection. A dose of 2.0 ml/lb inoculated 24 hours prior to the feeding of virus gave complete protection. Rhodes and Clark(5) reported an *in vitro* neutralization titer of approximately $10^{-3.5}$ for gamma globulin tested against Lansing virus in mice. Hammon, Cheever, and Sather(6) obtained some protection against poliomyelitis in suckling mice with gamma globulin in 0.05 ml/lb dose.

*Methods.* A rodent-adapted Y-SK strain* of poliomyelitis virus was employed. After 4 intracerebral passages through mice, virus-infected brains and spinal cords of 7 mice were harvested aseptically and emulsified in distilled water to a 10% suspension. This suspension was titrated by intracerebral inoculation of white mice. The $LD_{50}$ dose calculated at 21 days according to the Reed-Muench(7) formula, was $10^{-3.35}$. The 10% suspension

* Kindly provided by J. R. Paul.