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Combined Effects of Drugs and Electrical Excitation of Cortical Motor Area in Cats.*

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It was shown that, following the method of François-Franck,¹ between 35 and 55 clonic convulsions could be elicited in cats by stimulating the cortical motor area with the induced tetanizing current before the animals succumbed.² Wortis, Coombs and Pike³ observed that from about 5 to 10 clonic convulsions can be induced by the administration of convulsant drugs such as camphor monobromide before respiration fails and blood pressure falls to base line.⁴

In this series, which first developed as a set of controls in another group of experiments, I wished to see whether a combination of both methods would be more or less effective in prolonging or curtailing the number of convulsions and the resistance of the animal, than the use of one method alone.

Two methods of procedure were carried out.

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¹ François-Franck, 1887. *Léçons sur les fonctions motrices du cerveau*, Octave Doin, Paris.

² Coombs, H. C., *Am. J. Physiol.*, 1932, **100**, 65.

³ Wortis, S. B., Coombs, H. C., and Pike, F. H., *Arch. Neurol. and Psychiat.*, 1931, **26**, 156.

⁴ Coombs, H. C., and Pike, F. H., *Am. J. Physiol.*, 1931, **97**, 92.

1. In a series of 10 cats, the motor area was exposed under ether, and the anesthetic then intermitted. After recovery from ether, the cortex was stimulated with a mild induced tetanizing current as previously described. When the cortex had been stimulated from 25 to 40 times, with the usual clonic convulsions, a dose of camphor monobromide which corresponded to about the estimated minimal convulsive dose for the weight of the animal, was injected intravenously. In most cases, it proved fatal. Respiration failed and the animal usually died in tonic extension without the usual typical clonic convulsion, or with only a few clonic twitches.

2. In another series of 12 cats, after exposure of the motor area under anesthesia, with one electrical excitation to make sure the clonic convulsive response was readily elicitable, the estimated minimal convulsive dose of camphor monobromide or absinth was administered. When the convulsion due to the drug had worn off, the motor cortex was stimulated as before, until the animal succumbed, and it was found that the number of electrical excitations which could be done under these conditions had a range of from 10 to 20, with an average between 14 and 15—obviously far below the range of 35 to 55 convulsions which could be elicited in a similar way when no drug was given. Moreover, following a clonic convulsion elicited by a minimal dose of the convulsant drug, the response to electrical excitation was stronger than when electrical excitation only was done, the clonic convulsion sometimes lasting from 45 seconds to one minute, with clonic twitches persisting for another minute after the convulsion had ceased.

It has been shown in the case of convulsant drugs and cerebral anemia that when combined, the animal succumbs to a sum of less than half of each agent which would be fatal if used alone (Coombs and Pike⁵), that is, excitation from 2 different chemical sources appears to be more destructive to the cells of the central nervous system than a considerably greater amount of excitation from only one source. This appears to be the case also with excitation from a physical and a chemical source, *i. e.*, electrical excitation and camphor. Under these conditions, animals succumb to about one-third the number of electrical excitations plus about one-tenth the amount of the drug which, when taken separately, has been found to be lethal in a large number of cats.

In connection with work by Pike and Notkin⁶ on the summation of the effects of drugs, I may call attention to the following con-

⁵ Coombs, H. C., and Pike, F. H., *Am. J. Physiol.*, 1932, **99**, 521.

⁶ Notkin, J., and Pike, F. H., *Am. J. Psychiat.*, 1931, **10**, 771.

siderations. We have no measure of the work done either by the chemical agent or the physical agent in eliciting a convulsion. The mechanism of stimulation by chemical agents must differ in some essential respect from that of stimulation by physical agents since the sum of the 2 effects, *i. e.*, excitation by a chemical agent first, and then by a physical agent, or conversely, excitation by a physical agent first and then by a chemical agent, differs so widely from the total effect of either chemical or physical excitation alone. From the numerical ratio one might say that one chemical excitation will do about as much damage as several physical excitations and that the end result of the processes set up by either form of excitation renders the cells more vulnerable to the end result of processes set up by the other.

6332

Buffer Influence Upon Response of Striated Muscle to Caffeine Stimulation in Fatigue Studies.

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The experiments cited here indicate the influence of the buffered solvent upon the response of the gastrocnemius muscle of *Rana pipiens* Schreher with respect to caffeine action. In recognition of the importance of the pH factor upon physiological phenomena, this environmental variant was controlled at a constant value. It was noted, however, in studying the effect upon neuro-muscular responses in fatigue studies, that in spite of the constant pH conditions as maintained at 7.3, which is the pH of frog blood and lymph, definitely variable results were obtained. Even the complete reversal of the characteristic responses was observed in accordance with the nature of the buffer employed as the particular injection medium for the substance concerned.

The influence of ion variation on the action of different concentrations of Ca and K in a Locke solution medium upon smooth muscle action, as shown by Salant and Parkins,¹ demonstrates that the effect of an alkaloid—in their experiments ergotamine was

¹Salant, Wm., and Parkins, Wm. M., *J. Pharm. and Exp. Therap.*, 1932, 45, 315.