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Mechanism of the Emetic Action of the Chaulmoogrates.*

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Read[1] recently has cast doubt upon the finality of evidence previously advanced by himself[2] and others[3] as to the central emetic action of chaulmoogrates. The possibility of sufficient salivary secretion of chaulmoogrates to bring about local gastro-enteric irritation and reflex emesis negates conclusions drawn from observed effects of parenterally administered chaulmoogrates. It thus appears desirable to establish by criteria other than taste alone whether or not chaulmoogrates are present in saliva following therapy and also to study the nature of the emetic effect further.

Absence of rapid racemization of d-chaulmoogric acid in the body has been shown by Walker, MacArthur and Sweeney.[4] In the present experiments no traces of d-chaulmoogric acid were found polariscopically in ether-alcohol extracts of 5 to 10 cc. acidified saliva samples of dogs, cats and a human volunteer taken after oral administration of gelatine capsules of chaulmoogric acid in doses of 10 to 100 mg./kg. as the strongly dextrorotatory Na salt or ethyl ester. Concentrations to be effective *in vivo* in producing emesis would presumably exceed the 0.001 to 0.01 M solutions of Na chaulmoograte we have found active in stimulating isolated rabbit duodenum. Assuming a daily flow of 1400 cc. of saliva for a human, approximately one-fifth of the administered dose of 10 mg./kg. must then be excreted by the salivary glands to maintain a concentration of 0.01 M Na chaulmoograte in the saliva for one hour, which in itself appears improbable. Further, it is generally accepted

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1 Read, B. E., *Internat. J. Lep.*, 1933, **1**, 293.

2 Read, B. E., *J. Pharmacol. and Exp. Therap.*, 1924, **24**, 221.

3 Lissner, H. H., *Am. Rev. Tuberc.*, 1923, **7**, 257; Schwarz, L., *Z. nahr. Genussm.*, 1911, **22**, 441; Valenti, A., *Archiv. di Farmacol. sper. e Sci. aff.*, 1917, **24**, 23.

4 Walker, E. L., MacArthur, C. G., and Sweeney, M. A., *Trans. Nat. Tuberc. Assn.*, 1923, 553.

that tasting of injected substances does not presuppose excretion through the saliva.[5]

Other observations indicative of central action may be summarized briefly. In dogs, oral doses of 100 mg./kg. of ethyl chaulmoograte cause emesis in from 35 to 205 minutes, allowing time for sufficient absorption of chaulmoograte; vomiting does not relieve the nausea, and should the vomitus be re-eaten by the dog some time later, emesis does not then recur. Na chaulmoograte in doses of 67 mg./kg. causes emesis in dogs in an average time of 120 minutes although gastric irritation must be considerably greater than with either ethyl chaulmoograte or chaulmoogra oil. Dogs given emetic doses of chaulmoograte every third day respond by vomiting more readily; conditioning of the response was ruled out by giving an equal dose of olive oil in gelatine capsules as a control. In a dog vomiting within 35 minutes after an oral dose of 100 mg./kg. of ethyl chaulmoograte, 0.01 mg./kg. of atropine (sufficient to antagonize quantitatively one minimal emetic dose of pilocarpine) delayed emesis to 85 minutes. Two-tenths mg./kg. of atropine delayed emesis to 180 minutes, and if 0.2 mg./kg. of atropine were given with 100 mg./kg. of ethyl chaulmoograte and the same dose of atropine repeated once at 20, 40 or 80 minutes, no emesis occurs. For cats the findings were essentially the same; oral doses of 75 mg./kg. of Na chaulmoograte brought about emesis in an average time of 83 minutes although administration of 100 mg./kg. of ethyl chaulmoograte produced extreme nausea but did not result in emesis in 7 of 9 trials with 6 cats even when given on the day following administration of the same dose. Two of 9 cats so treated vomited in 65 and 87 minutes. One hundred and fifty mg./kg. of ethyl chaulmoograte produced emesis within an average time of 92 minutes in 6 of 6 cats. Intramuscular administration of the standard dose[6] of nicotine abolished the emetic response to ethyl chaulmoograte. Again, with dogs an emetic dose of morphine given one hour prior to 100 mg./kg. of ethyl chaulmoograte prevented emesis, while an emetic dose of apomorphine, which does not have a secondary depressing effect on the vomiting center as does morphine,[7] given similarly did not prevent the emetic response.

[5] Winternitz, M., Deutsch, J., and Burell, A., *Mediz. Klinik.*, 1931, **27**, 986; 1932, **28**, 831; Tarr, L., Oppenheimer, B. S., and Sager, R. V., *Am. Heart J.*, 1933, **8**, 766.

[6] Hatcher, R. A., and French, B. S., *J. Pharmacol. and Exp. Therap.*, 1932, **46**, 97.

[7] Leake, C. D., *J. Pharmacol. and Exp. Therap.*, 1922, **20**, 359.

In a human volunteer 5 mg./kg. of ethyl chaulmoograte administered orally in a gelatin capsule was tolerated with some nausea but no emesis, while 10 mg./kg. brought about emesis in 63 minutes. Dr. H. I. Cole has told us that he has observed patients tolerant to 5 cc., or about 100 mg./kg., of ethyl chaulmoograte after taking this agent orally for some time.

Among the many peculiar pharmacological actions of *Cannabis sativa* is its rôle in the *Tai-Fong-Chee* oral method of administering chaulmoograte recommended by Travers.[8] Travers reports a mixture of 2 parts of powdered Hydnocarpus nut and 1 part of *Cannabis indica* to be well tolerated by humans. We have found 5 of 5 cats tolerate 200 mg./kg. of ethyl chaulmoograte if 100 mg./kg. of fluid extract of Cannabis is given simultaneously or previously.

Summary. Evidence is presented indicating that the emetic effect of the chaulmoograte is central. The action of Cannabis, atropine and morphine in abolishing the emetic response in dogs and cats is reported.

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An Inexpensive Tissue for Biological Testing.

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For some time we have been interested in reactions of the iris to various reagents and have observed that a strip of sphincter pupillae of the steer iris affords an excellent preparation for studying the effects of many drugs on unstriated muscle and its innervation. We suggest the adoption of this tissue for pharmacological studies because of its inexpensiveness, certainty and sensitivity of response, availability at any abattoir and its viability even after 3 to 7 hours post mortem. Precautions regarding preparation of iris strips are given elsewhere.[1, 2]

Besides demonstrating the antagonistic relaxing action of various concentrations of atropine against sphincter contraction by physostigmine one is able to produce opposite effects with histamine and

8 Travers, E. A. O., *Proc. Roy. Soc. Med.*, 1926, **19**, 1.

1 Miller, G. H., *J. Pharm. and Exp. Therap.*, 1926, **28**, 219.

2 Yonkman, F. F., *J. Pharm. and Exp. Therap.*, 1930, **40**, 195.