12. ———, *Medicine,* 1947, v26, 441.
13. ———, *Am. J. Pub. Health,* 1944, v34, 335.
14. ———, *J. Clin. Invest.,* 1947, v26, 957.
15. Bell, J. A., Rowe, W. P., Engler, J. I., Parrott, R. H., and Huebner, R. J., *J.A.M.A.,* 1955, v157, 1083.
16. Rowe, W. P., Hartley, J. W., and Huebner, R. J., PROC. SOC. EXP. BIOL. AND MED., 1956, v91, 260.
17. Jawetz, E., *Science,* 1955, v122, 1190.
18. Dascomb, H. E., and Hilleman, M. R., *Am. J. Med.,* in press.
19. Huebner, R. J., Bell, J. A., Rowe, W. P., Ward, T. G., Suskind, R. G., Hartley, J. W., and Paffenbarger, R. S., *J.A.M.A.,* 1955, v159, 986.
20. Hilleman, M. R., Tousimis, A. J., and Werner, J. H., PROC. SOC. EXP. BIOL. AND MED., 1955, v89, 587.

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Effects of Mescaline in Laboratory Animals and Influence of Ataraxics on Mescaline-Response. (22485)

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Mescaline has been of continuing interest to biologists because of its ability to produce "model psychosis" in man(1) as well as experimental catatonia in laboratory animals (2). Current interest has been stimulated by the findings that α-(4-piperidyl)benzhydrol HCl (azacyclonol, Frenquel) antagonizes mescaline-induced hallucinosis in man(3,4), electroencephalographic changes in man(5) and rabbits(6), and spasm of isolated estrus-rat uteri(7). Because of preliminary clinical reports on the beneficial effects of azacyclonol in mentally-disturbed patients, this drug has been included in a category of drugs known as "ataraxics" or "tranquilizers" together with reserpine and chlorpromazine(4). The present study was undertaken, first, to determine whether or not reasonably objective indications of behavioral response could be obtained following mescaline in laboratory animals and, second, to study the ability of ataractic compounds to antagonize the effects of mescaline on behavior.

Materials and methods. Mescaline sulfate was administered to dogs and cats intravenously, intraperitoneally, and into the lateral ventricle of the brain after the method of Feldberg and Sherwood(8,9). Permanent intraventricular cannulae of stainless steel were implanted in the cranium and covered with a skin-flap, placement being confirmed by x-ray or dissection following death or sacrifice. These cats showed no apparent ill effects from the cannulae. Routinely, antibiotics (500 mg dihydrostreptomycin and 100,000 U penicillin G, intramuscularly) were administered for 3 days after operation, as well as the day of and day after each intraventricular experiment. These experiments were not begun until at least one week after operation and the cats were rested 5-10 days between tests. Drugs were administered intraventricularly in volumes of 0.5 ml or less under sterile conditions, with the cats held under minimal restraint. The volume of the cannulae was approximately 0.1 ml.

Results. Intravenous mescaline in dogs. In 6 experiments on 4 dogs, 20 mg/kg of mescaline caused repeated defecation and urination, tachypnea, salivation, mydriasis, and apparent dizziness. These effects lasted 10-20 minutes and were succeeded by a 4-hour period during which the dogs lay or stood nearly motionless in one place, exhibiting marked disregard for and non-reactivity to visual, auditory, and pain stimuli. This condition resembled that in cats described by de Jong(2), which he termed "catatonia," as well as that recently described in dogs by Hosko and Tislow(10); it also duplicated some of the effects of mescaline in man, such as salivation, emesis, mydriasis, immobility, and decreased reactivity to pain(2,11,12). When the dogs were forced to move, they

stepped slowly and gingerly, but without signs of ataxia or hypotonia. There was no apparent tolerance in 2 dogs on whom the experiment was repeated 24-48 hours later. Three of the dogs were subsequently pretreated with 50 mg kg azacyclonol and then given mescaline 1 hour later. Azacyclonol caused no gross effects itself, but after mescaline the dogs became quiet, one of them vomiting and panting, and another urinating; all were completely normal in 5-15 minutes. It appeared that the catatonic response to mescaline had been prevented by azacyclonol.

Intraperitoneal mescaline in cats. For comparison, the effect of 50-75 mg/kg mescaline was observed in 6 experiments on 4 cats. They developed autonomic signs (salivation, emesis, tachypnea, mydriasis) and behavioral signs (progressive depression leading to catatonia). The latter resembled the "catalepsy" and "negativism" in cats described by de Jong (2) following doses of more than 25 mg/kg intramuscularly.

Intraventricular mescaline in cats. After the foregoing initial studies, it was decided to restrict experimentation to drugs administered by this route, primarily to concentrate on reactions in the central nervous system. Mescaline was injected 21 times in 18 cats in doses ranging from 1-3 mg in 0.5 ml sterile 0.5% saline. Injection of saline alone caused no appreciable effect. Immediately after mescaline, the cats began a loud, continuous yowling that was unlike any normal cat-sound and that could usually be precipitated, if it did not begin spontaneously, by a sudden, loud noise. During the next 20 minutes, there was in addition a succession of salivation, tachypnea, retching, lacrimation, defecation, urination, and mydriasis. Of these signs, yowling, salivation, tachypnea, retching, and defecation occurred in every cat; the remainder occurred in the majority. The facial expressions were very similar to those depicted by de Jong(2). The cats displayed a decreasing interest in the environment and could be stimulated to move only with difficulty ("negativism"); this condition began to develop at about 10 minutes and lasted for 4 or more hours. Body movements were slowed and somewhat ataxic when the cats were forced to jump or walk; following this, they quickly resumed their stuporous immobility. This depressed state was more severe than the ataraxia produced by intramuscular chlorpromazine (20 mg/kg) or intraperitoneal reserpine (0.5 mg/kg) in cats, and again corresponded more closely to the syndrome of "decreased motor initiative, negativism, and catalepsy"(2). There was, however, no evidence of complete plastic rigidity, as is commonly caused by bulbocapnine (2,13). These autonomic and psychomotor effects of mescaline will be referred to below as the "mescaline-response."

Five cats that instantaneously caught, killed, and ate a mouse several hours before intraventricular mescaline were each offered another mouse 30 minutes afterwards. The cats at first ignored the mice, one of them even submitting placidly to having his ears and nose nibbled. Later, the cats began to regard them with curiosity; they appeared to derive enjoyment from rubbing their cheeks against the mice and allowing them to crawl over and under their bodies. This behavior was interrupted by periods of immobility and persisted until some 18-20 hours later (only 3 hours in 1 cat), at which time the "fondling" became progressively more rough, ending with a typical "cat-and-mouse" play in which the mice were killed and eaten. Presumably, this progression in behavior was associated with clearance of the drug. A sixth cat, which normally was not a "mouser," displayed similar "fondling" behavior towards mice while under the influence of mescaline; moreover, his normally antagonistic attitude towards human beings was softened into a playful tractability and friendliness. The failure of catatonic cats to attack mice was lucidly depicted by de Jong(2) for a case of acetylcholine-catatonia.

It is noteworthy that the paroxysms of scratching noted by Schwartz and co-workers in 3 cats(30) were not observed in any appreciable number of cats we have injected with mescaline to date. The reason for this discrepancy is not at once apparent.

Reserpine and the mescaline-response. In this and the following experiments, cats were

used that had previously been standardized on mescaline. The immediate effects of reserpine (0.1 mg intraventricularly in 4 cats) were variable and included 2 cases each of meowing as if in pain, mydriasis, defecation, and mild ataraxia or drowsiness and indifference. One cat had generalized tremors and appeared dizzy; another cat salivated. These effects were mild and the cats seemed completely normal 2 hours later. It is noteworthy that these cats had not yet displayed the well-known signs that always follow 0.05-0.1 mg/kg reserpine given intraperitoneally: miosis, nictitating membrane relaxation, and an ataractic state approaching the stupor of catatonia.

Approximately 2 hours after intraventricular reserpine, 2 mg mescaline were administered similarly. The cats developed the immediate symptoms of mescaline intoxication (yowling, tachypnea, defecation), but failed to progress into a state of catatonia. By 5 hours after injection, the cats were developing miosis and were somewhat less active than usual, *i.e.*, mildly tranquil. The following day they showed the typical residua that result from reserpine: miosis, nictitating membrane relaxation, anorexia, diarrhea, and tranquility or ataraxia. This experiment suggested that reserpine pretreatment antagonized the development of mescaline-catatonia.

Chlorpromazine and the mescaline response. Chlorpromazine (2 mg intraventricularly in 2 cats) caused nictitating membrane relaxation, tachypnea, ataxia, and a marked catatonia, wherein the cats appeared oblivious of visual, auditory, and pain stimuli and maintained abnormal positions (catalepsy). Approximately 2½ hours later, 2 mg mescaline were injected similarly. The only discernible change was a deepening of the catatonia and a dilatation of the pupils. Since these cats were already catatonic when mescaline was administered, the results from mescaline were inconclusive. Therefore, the experiment was repeated in 4 additional cats injected with 1 mg chlorpromazine. This dose level quieted all 4 cats and caused mild ataxia and nictitating membrane relaxation in 2; all were completely normal 2-3 hours later when 2 mg mescaline were administered. The only response to mescaline observed was a moderate decrease in spontaneous activity. This second experiment suggested that pretreatment with doses of chlorpromazine, which in themselves caused no appreciable effect, almost completely blocked the mescaline-response. The effects of higher doses of chlorpromazine given intraventricularly were similar, but not identical, to those following intramuscular injection (5-20 mg/kg): nictitating membrane relaxation, moderate miosis, marked ataxia, and a non-cataleptic state of ataraxia.

Azacyclonol and mescaline-response. Three cats received 4 injections of 5 mg each of azacyclonol intraventricularly and 2 received 1 mg. The first 3 cats responded with tachypnea, emesis, tremors, nictitating membrane relaxation, ataxia, and a moderate degree of ataraxia. The latter 2 cats responded with tachypnea, ataraxia, and in 1 case emesis. In no case was there evidence of hyperkinesis, as produced by high parenteral doses (14). All of the cats were substantially normal except for residual ataxia when injected 2½ hours later with 2-3 mg mescaline intraventricularly. None of the autonomic responses to mescaline was blocked (see 3,6), but the psychomotor responses were altered from a catatonic to an excitatory type in 4 of the 5 cases ("crying," tremors, attacking, hissing, running, restlessness, and in 1 cat convulsions). This state of excitation passed into one of ataraxia in 1 cat, resembling that seen in the cat that failed to show any excitation at all. Another test was modeled after Fabing's experiment on the blockade of d-lysergic acid diethylamide (LSD)-psychosis in man by azacyclonol prophylaxis(3). Two cats received 5 mg azacyclonol intramuscularly each day for 5 days and, on the 6th day, a final 5 mg 2 hours before the intraventricular injection of mescaline. One cat displayed the typical yowling, mydriasis, tachypnea, and catatonia for 80 minutes after 2 mg mescaline; the other cat panted, defecated, and remained ataractic for 30-45 minutes after 1 mg. Both were completely normal 2 and 1 hours later, respectively, suggesting a decreased duration of response to intraventricu-

lar mescaline following chronic azacyclonol prophylaxis.

Discussion. In dogs and cats, mescaline injected intravenously or intraperitoneally produced a prolonged period of catatonic immobility that was apparently prevented in the former by pretreatment with azacyclonol. When injected into the lateral ventricle of the cat's brain, mescaline caused a characteristic yowling, various autonomic effects, and catatonia. It has been our experience that a certain degree of tolerance is developed by cats injected every 10-14 days with mescaline: the minimal effective dose for marked catatonia increased from approximately 1.5 to 2.5 or 3.0 mg. This did not appear to be true for the convulsive dose, however, which remained slightly over 3.0 mg. Pretreatment intraventricularly with ataraxics had the following apparent influences on the mescaline-response: reserpine antagonized the development of catatonia, chlorpromazine almost completely inhibited all of the responses to mescaline, and azacyclonol tended to change the catatonic mescaline-response into an excitatory type. The reactions of cats to intraventricular reserpine and azacyclonol alone differed from those typically appearing after intraperitoneal or intravenous administration, while the reactions to chlorpromazine were similar. Moreover, the effects of intraventricular mescaline were different from those of intraventricular LSD(15,30) and the effects of intraperitoneal or intramuscular reserpine were different from those of intraventricular 5-hydroxytryptamine (serotonin)(16,30).

A certain amount of care should be exercised in the interpretation of the foregoing experimental results and conclusions, since the observation and classification of behavioral responses were always necessarily subjective. At high dose levels, we were not at all certain that a clear distinction could be made, for example, between catatonic stupor and marked ataraxia. Therefore, we attempted to use doses of ataraxics that were low enough to render the cats essentially normal by the time mescaline was administered.

The mescaline-blocking action of chlorpromazine suggested by these studies is consistent with previous findings that this drug antagonized the psychotic effects of mescaline and LSD in human volunteers(11,17,18) and the electroencephalographic changes caused by LSD(19). The results with azacyclonol are consistent with the reports that it antagonized hallucinogen-induced psychoses(3,4), electroencephalographic changes(5,6), and *in vitro*-uterospasm(7). Moreover, all 3 ataraxics have shown promise in the therapy of mental illness.

It is noteworthy that the 3 ataraxics employed in this study are serotonin-blockers, while small amounts of mescaline and LSD are serotonin-potentiators(20). This suggested to Costa(20) that, in general, hallucinogens may potentiate and ataraxics may antagonize serotonin in the brain, thereby producing their characteristic psychic effects. Dosage, however, is an important consideration, for it is well-known that larger amounts of LSD block serotonin(20). The situation is further complicated by the facts that large amounts of serotonin and reserpine, which releases bound - serotonin(21-23), potentiate hexobarbital-hypnosis in mice and that this potentiation is reversible by huge doses of LSD(21,24), but not by mescaline(25). Hexobarbital-potentiation is also a property of iproniazid(25), a compound that prevents the destruction of serotonin by monamine oxidase(26). Although chlorpromazine is also a potentiator(27), it does not appear to be a serotonin-releaser(28); moreover, the potentiation is not reversible by LSD(29). Azacyclonol was reported to potentiate hexobarbital in mice(14), but neither Shore(29) nor we (unpubl. data) have been able to confirm such activity at moderate dose-levels. The foregoing observations emphasize certain differences among the ataraxics, as well as between mescaline and LSD. These considerations, among others, suggest that these ataraxics may have different mechanisms of psychic action.

Summary. Mescaline, injected intravenously and intraperitoneally into dogs and cats and into the lateral ventricle of the brain of cats, produced acute autonomic effects followed by catatonia. These responses ap-

peared to be altered or prevented by pretreatment with the ataraxic agents chlorpromazine, reserpine, and azacyclonol.

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1. Hoch, P. H., Cattell, J. P., and Pennes, H. H., *Am. J. Psychiat.*, 1952, v108, 579.

2. De Jong, H. H., *Experimental Catatonia*, Williams & Wilkins, Baltimore, 1945.

3. Fabing, H. D., *Science*, 1955, v121, 208.

4. ———, *Neurology*, 1955, v5, 319.

5. Himwich, H. E., *Sci. Am.*, 1955, v193, No. 4, 80. (Also see: Sargent, W., cited in *J. Am. Med. Assoc.*, 1956, v161, 265.)

6. Rinaldi, F., and Himwich, H. E., *Science*, 1955, v122, 198.

7. Van Arman, C. G., and Sturtevant, F. M., unpublished data, 1955.

8. Feldberg, W., and Sherwood, S. L., *J. Physiol.*, 1954, v123, 148.

9. Feldberg, W., *Proc. Roy. Soc. Med.*, 1955, v48, 853.

10. Hosko, M. J., and Tislow, R., *Fed. Proc.*, 1956, v15, 440.

11. Schwartz, B. E., Bickford, R. G., and Rome, H. P., *Proc. Staff Mtngs. Mayo Clin.*, 1955, v30, 407.

12. Wikler, A., *J. Nerv. Ment. Dis.*, 1954, v120, 157.

13. Feldberg, W., and Sherwood, S. L., *Brit. J. Pharm. Chemother.*, 1955, v10, 375.

14. Brown, B. B., Feldman, R. F., and Braun, D. L., *Fed. Proc.*, 1955, v14, 322.

15. Sturtevant, F. M., and Drill, V. A., *Anat. Rec.*, 1956, in press.

16. Sturtevant, F. M., and Drill, V. A., *ibid.*

17. Hoch, P. H., *Am. J. Psychiat.*, 1955, v111, 787.

18. Denber, H., and Merlis, S., *Trans. Soc. Biol. Psychiat.*, 1955, v10, 36.

19. Bradley, P. B., and Rance, A. J., *J. Physiol.*, 1955, v129, 50P. (Also see: Elkes, cited in *J. Am. Med. Assoc.*, 1956, v161, 265.)

20. Costa, E., PROC. SOC. EXP. BIOL. AND MED., 1956, v91, 39.

21. Shore, P. A., Silver, S. L., and Brodie, B. B., *Science*, 1955, v122, 284.

22. Pletscher, A., Shore, P. A., and Brodie, B. B., *ibid.*, 1955, v122, 374.

23. Brodie, B. B., Pletscher, A., and Shore, P. A., *ibid.*, 1955, v122, 968.

24. Shore, P. A., Silver, S. L., and Brodie, B. B., *Experientia*, 1955, v11, 272.

25. Sturtevant, F. M., *Naturwissenschaften*, 1956, v43, 67.

26. Zeller, E. A., Barsky, J., and Berman, E. R., *J. Biol. Chem.*, 1955, v214, 267.

27. Brodie, B. B., Shore, P. A., and Silver, S. L., *Nature*, 1955, v175, 1133.

28. Pletscher, A., Shore, P. A., and Brodie, B. B., *J. Pharm. Exp. Therap.*, 1956, v116, 46.

29. Shore, P. A., personal communication, 27 Sept. 1955.

30. Schwarz, B. E., Wakim, K. G., Bickford, R. G., and Lichtenheld, F. R., *Arch. Neurol. Psychiat.*, 1956, v75, 83.

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Similarity of Effect of "Adrenalin", Adrenaline and Nor-Adrenaline on the Cat Denervated Heart.* (22486)

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In view of the current interest in and conflict of evidence as to possible similarity or difference in action of adrenaline and noradrenaline, these have been tested as to their effect on the acutely surgically denervated heart of the cat. This report describes the chronotropic effect of extracted glandular adrenaline and of synthesized l-adrenaline and l-nor-adrenaline on this preparation.

Methods. Fasted cats, males and females, were anesthetized with Dial-Urethane (Ciba), 0.6 cc/kilo of body weight injected intraperitoneally. The heart was denervated by vagal section and removal of the stellate ganglia as first described by Levy(1); blood pressure and heart rate were recorded by mercury manometer from the left carotid artery; injec-

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