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Spasmolytic Action of Dolophine (Amidone).*

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(Introduced by Nilkanth M. Phatak.)

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Amidone (6 dimethylamino-4, 4, diphenyl-3-heptanone) is a new synthetic analgesic compound related to demerol (Dolantin) originally prepared at the I.G. Farbenindustrie research plant at Hoechst am Main and first described in this country in the U. S. State Department Technical Intelligence Team Report.¹ Scott and Chen² reported that this agent had marked analgesic properties when tested in both dogs and humans by the Wolff-Hardy technic as well as a comparatively low toxic/analgesic ratio. Later, these workers named the compound "dolophine" and reported the clinical trial of 4 related compounds.³ They also found that "dolophine" possessed about equal spasmolytic action when compared with demerol on isolated intestinal strips. Karr⁴ found decreased propulsive activity of the intestines of rats and rabbits after "dolophine" which was slightly more marked than the decrease noted after demerol. We have further studied the action of these spasmolytic agents on isolated intestinal strips and, in addition, have compared their effects on the isolated uterine musculature of rabbits and rats.

Method. The usual technic for recording contractions of isolated muscle strips was used. Furfuryl trimethyl ammonium iodide (Furmethide)⁵ served as the spasmogenic

agent for the rabbit intestinal strips and the rat uteri. Methyl ergonovine (Methergine)⁶ was used to stimulate contraction in rabbit uterine strips. Other agents were also used for stimulating contraction.

Results. "Dolophine" and demerol produced about the same degree of spasmolysis on the isolated rabbit intestine when equal concentrations of the drugs were used, with concentrations as low as 0.025 mg/50 cc (1:2,000,000) being effective. These results for demerol agree with other reports.^{7,8,9}

The contracted rat uterus showed a similar relaxation when concentrations of either drug as low as 1:2,000,000 were used. Rabbit uteri, however, required more "dolophine" than demerol for spasmolysis on most trials, the least effective concentration being 0.075 mg/50 cc (1:666,666). Normally active smooth muscle strips were found to respond irregularly to both drugs.

The pharmacodynamic basis for the spasmolytic action of these compounds is not fully known. Since "dolophine" lysed spasm induced by both musculotropic (Methergine, Barium, Pitressin) and neurotropic (Furmethide, Neostigmine, Acetylcholine) spasmogenic agents, its action is probably largely musculotropic. In this respect it resembles trasentin, which, in addition to a musculotropic spasmolytic action, shows some local anesthetic properties. A recent report¹⁰ in-

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¹ Kleiderer, E. C., Rice, J. B., Conquest, V., and Williams, J. H., Report 981, Office of the Publication Board, Department of Commerce, Washington, D.C.

² Scott, C. C., and Chen, K. K., *J. P. E. T.*, 1946, **87**, 63.

³ Scott, C. C., Kohlstaedt, K. G., and Chen, K. K., *Anesth. and Analges.*, 1947, **26**, 12.

⁴ Karr, N. W., *Fed. Proc.*, 1947, **6**, 343.

⁵ Fellows, E. J., and Livingston, E. A., *J. P. E. T.*, 1940, **58**, 231.

⁶ Kirchhof, A. C., Racely, C. A., Wilson, W. M., and David, N. A., *West. J. Surg., Gyn. and Obs.*, 1944, **52**, 197.

⁷ Yonkman, F. F., Noth, P. H., and Hecht, H. H., *Ann. Int. Med.*, 1944, **21**, 7.

⁸ Climenko, D. R., *Fed. Proc.*, 1942, **1**, 15.

⁹ Yonkman, F. F., *Anesth. and Analges.*, 1944, **23**, 207.

¹⁰ Way, E. L., *Science*, 1945, **101**, 566.

dicates that demerol, like trasentin, has local anesthetic properties and Everett¹¹ in this laboratory has demonstrated that "dolphine" produces local anesthesia in the rabbit's cornea. Thus, the local anesthetic property, as well as musculotropic spasmolysis seems to be common to trasentin, demerol and "dolphine."

¹¹ Everett, F. G., personal communication.

Summary. Isolated strips of rabbit intestine and rat and rabbit uteri respond with spasmolysis when treated with "dolphine" and demerol when spasm is induced with furmethide or Methergine. The ratio of spasmolytic concentration is approximately 1:1 although rabbit uteri required slightly more dolophine than demerol for spasmolysis.

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Induction of Male Copulatory Behavior in the Brown Leghorn Hen.*

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Previous experiments have shown that daily injections of testosterone propionate in poulards¹ and pullets² will induce masculinization of somatic sex characters and behavior. These individuals crowed, became combative, and displayed male courtship but no copulatory behavior, even though injections were continued for periods up to 7 months. The absence of this phase of behavior has long baffled investigators in view of the ease with which other sexual characters may be masculinized in the fowl. Two incidental cases are recorded^{3,4} in which hens revealed male copulatory behavior, although neither instance is based on extensive experimentation. The present experiments, in progress for over 4 years, show that masculine copulatory behavior may be induced and maintained in some pullets following suc-

cessive implantations of androgen pellets.

Each of 4 non-laying pullets (A, BW, G, and GA) received subcutaneous implantations of testosterone propionate pellets (average weight, 33.4 mg) when 5 months old and subsequently at 84, 164, 244, 337, 425, 530, 630, and 727 days. Two control pullets (B and W) received implantations of cholesterol pellets averaging 32.6 mg. Pellet implantations were repeated upon absorption, determined by palpation and comb regression. The behavior was tested, generally on alternate days, by introducing each bird, alone in its pen, to a female, to a male, or to a dummy female mounted in the squatting, copulatory position.

Experimental pullet A was first observed to crow at 34 days, to chase, grab, and attempt mounting at 95 days, to grab, mount, and copulate at 110 (age 262), and to waltz and circle at 114 days after the first implant. Pullet BW was also first observed to crow at 34, chase, grab, and attempt mounting at 95, mount and copulate at 103 (age 255), and waltz and circle at 127 days. A continued to copulate for 5 months, when it died, and BW for 8 months after the final implant. Courtship activity preliminary to copulation, never very vigorous, was frequently absent. In no instance did they indicate receptivity by squatting at the approach of the male.

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¹ Davis, David E., and Domm, L. V., *Proc. Soc. Exp. Biol. and Med.*, 1941, **48**, 667; *Essays in Biology*, University of Calif. Press., 1943, 171.

² Domm, L. V., Davis, David E., and Blivaiss, Ben B., *Anat. Rec.*, 1942, **84** (Suppl.), 31.

³ Domm, L. V., *J. Exp. Zool.*, 1927, **48**, 31.

⁴ Zitrin, A., *Endocrinology*, 1942, **31**, 690.