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Antagonism between atropin and certain central emetics.

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The minimal certainly emetic vein dose of pilocarpin alkaloid (hydrochloride used) was determined for dogs as 0.7 mg. per kilo. It having previously been observed that atropin was capable of antagonizing the emetic action of pilocarpin, experiments were made to determine the smallest dose of this alkaloid (sulphate used) which was just sufficient to prevent emesis from the minimal emetic dose of pilocarpin. The antagonistic dose of atropin alkaloid was then determined for twice, four, eight and sixteen times the minimal dose of pilocarpin.

The results showed that it requires about 1/75th as much atropin base as of pilocarpin base to antagonize the emetic action of the smallest effective dose of the latter. About the same ratio was found for twice the dose of pilocarpin. For four times the minimal dose of pilocarpin 1/95th as much atropin was required; for eight times about 1/125th; and for sixteen times about 1/200th.

Similar experiments were made with nicotin and atropin, but the toxicity of the former drug prevented the use of amounts larger than the minimal emetic dose. Atropin was found to antagonize nicotin in the proportion of about 1 : 70 (both in terms of base).

Other emetics previously shown to cause vomiting through central action were tested with atropin in doses up to 5.0 mg. of the base per kilo, or 500 times the effective dose against pilocarpin and 1,000 times that against nicotin. In no case was there any antagonism demonstrable. The drugs used were apomorphin, morphin, ouabain and emetin.

It has been shown[1] that pilocarpin produces emesis through a direct central action and since section of the vagi does not increase the minimal emetic dose, a local action of the drug in producing emesis seems very improbable. The antagonism of atropin,

[1] Eggleston, C. and Hatcher, R. A., *Jour. Pharm. and Exp. Ther.*, 1915, VII, 225.

therefore, would seem to be a central one, probably in the nature of a depression of certain central structures concerned with the vomiting act, or of certain paths to or from the central mechanism. It should be stated that the dose of atropin required to antagonize the minimal emetic dose of pilocarpin is insufficient to dilate the pupil and does not appreciably diminish the salivation or diarrhea produced by the pilocarpin. The mechanism of antagonism between atropin and nicotin is apparently the same as between atropin and pilocarpin, and it is interesting to recall the fact that nicotin and pilocarpin—the only central emetics which we have found so far to be antagonized by atropin—are very closely related in their pharmacologic actions.

Atropin is stated to be capable of preventing the emesis often seen following the therapeutic use of morphin in man and that induced in dogs. The mechanism of this action is usually given as involving a local action of both drugs on the stomach, morphin emesis being ascribed largely to a marked stimulation of the motor endings of the vagus in the stomach, which are depressed by atropin. In dogs, at least, morphin has been shown[1] to produce emesis through a central action and we have not been able to prevent this action by atropin in any dose. This failure confirms the observations of Guinard,[2] who, however, conceded some antagonistic action between atropin and morphin in man, which he thought due to a synergistic central depressant action of the two drugs.

The failure of atropin to antagonize the central emetics studied, other than pilocarpin and nicotin, raises several interesting points regarding the physiology of vomiting. We are all aware of the number and diversity of ways by which vomiting may be induced and of the existence, therefore, of many afferent paths for the stimulation of the central vomiting mechanism. It is suggested, on the basis of the present observations, that atropin antagonizes nicotin and pilocarpin on the one hand by depressing some limited portion of the vomiting center, and on the other hand fails to antagonize the other centrally acting emetics used since these may possibly influence the central mechanism through other and different portions.

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[1] *Loc. cit.*

[2] *Lyon Medical*, 1895, LXXX, pp. 37 and 49.

Experiments were also conducted using hyoscyamin in place of atropin, and others are now under way covering some of the other drugs with central emetic actions. The results of all of these will be detailed in the complete paper to be published later.

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The distribution of the fat soluble A, the growth-promoting substance of butter fat, in the naturally occurring foodstuffs.[1]

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That butter fat and egg yolk fats contain a substance whose chemical nature is unknown, which is indispensable for growth or prolonged maintenance of health was first pointed out by McCollum and Davis. Later they showed the presence of this substance in the maize kernel and in wheat embryo, and presented some evidence that if it is found in the oat kernel it is in very small amount.[2] Our further studies have confirmed these observations.

McCollum and Kennedy[3] have discussed the desirability of employing the term "fat-soluble A" for this, to distinguish it from the "water-soluble B," a substance which is widely distributed in the natural foodstuffs of both animal and vegetable origin and is likewise indispensable for growth or prolonged maintenance. The water-soluble B only is concerned with the production and cure of polyneuritis in pigeons.

Our experimental work with the grains has shown that the content of the fat-soluble A is greater in the maize kernel than in wheat, and greater in wheat than in the oat kernel. In all three the content is too low to induce growth at the maximum rate even though all other factors in the diet be near the optimum.

[1] Published with the permission of the Director of the Wisconsin Experiment Station.

[2] McCollum and Davis, *Jour. Biol. Chem.*, Vol. 15, p. 167 (1913); Vol. 21, p. 179 (1915); Vol. 23, pp. 181 and 231 (1915).

[3] McCollum and Kennedy, ibid., vol. 24, p. 491 (1916).