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The action of morphine, heroin, and codeine on respiration.

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In a previous series of experiments[1] on cats, it was found that the action of morphine and heroin on respiration was practically limited to a selective depression of the expiratory mechanism, and that codeine produced only stimulation of the spinal cord. These experiments were repeated upon decerebrated and anesthetized dogs, and upon anesthetized rabbits, inducing active expiratory efforts by inhalations of a constant CO_2-air mixture, and recording them by means of a record of intrathoracic pressure, using an esophageal balloon or a pleural cannula; blood pressure and respiratory volume were also recorded.

The results confirm those obtained with cats, namely, morphine and heroin have a selective action on the expiratory mechanism of dogs and rabbits as well as cats, while no constant depressant action could be detected with codeine.

With morphine, dogs showed passive expiration after 2 to 6 mg. per kilo, as a rule, and larger doses had no further effect until circulation was depressed; occasionally very large doses—300 mg. per kilo—reversed this effect and produced increased reflex excitability, but convulsions did not occur, even in decerebrated animelas. Depth of respiration was often increased as the rate was slowed. With rabbits, expiratory depression began with 1 mg. of morphine and was usually complete after 3 to 5 mg., but depth was more frequently decreased than was the case with dogs. Larger doses sometimes reversed this effect, and caused increased reflex excitability, with a return of active expiration, but the circulation of the rabbit was not depressed as much by morphine as was that of the dog or cat.

With heroin, 0.05 mg. per kilo sometimes made expiration completely passive in the dog, and depth of breathing was usually increased as the rate was slowed. Larger doses depressed circu-

[1] Schmidt and Harer, *J. Exp. Med.*, 1923, xxxvii, 47 and 69.

lation but had no further direct effect on respiration. In one experiment heroin depressed circulation but not respiration, and tetanic convulsions followed 80 mg. per kilo. In rabbits, expiratory depression and slowing of the rate of breathing began with 0.125 mg., and 0.25 to 0.5 mg. usually produced maximal slowing, though expiration was somewhat active when the rate was slowed, and depth was often decreased, but the slowing could always be completely removed by emptying the lungs more completely, as by pressure on the chest, suction on the tracheal cannula, or a partial pneumothorax. Apparently the expiratory efforts were too weak to arouse excitatory reflexes in the lungs, or the inspiratory cells were also depressed. Heroin also had less depressant action on the circulation of the rabbit than on that of the dog or cat.

Codeine, in dosage from 0.1 mg. to over 100 mg. per kilo, failed to slow respiration or make expiration passive in dogs or rabbits, and tetanic convulsions were the only definite result. In one recent experiment on a decerebrated cat, 5 mg. of codeine produced slowing and expiratory depression, but 25 mg. were required to remove the expiratory response to CO_2, while convulsions followed 35 mg.

It appears, therefore, that a selective depression of expiration is the characteristic action of morphine and heroin on the respiration of dogs and rabbits as well as of cats, though this action is not as clean-cut in the rabbit as in the other animals. That this effect may be responsible for the selective action of these drugs on the rate of breathing is shown by the acceleration which follows more complete emptying of the lungs, and this has been consistently observed in dogs and rabbits, as well as in cats, when the rate was slowed by morphine or heroin. It is possible that a similar selective action on expiration may explain the specific action of these drugs in cough and dyspnea in man. Codeine may possess a similar action on expiration, but it is certainly weaker and is usually masked by the action of the drug on the spinal cord.