

Toxic Levels of Morphine for the Hamster.*

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In the search for a conveniently small animal in which morphine addiction might be developed preparatory to a study of its effect on tissue metabolism, the hamster was found to be so resistant to the drug that the extremely high lethal dose was thought to be worthy of note. Coincidentally, the toxic symptoms observed differed from those reported in the literature for other species.¹

The present communication describes the toxic effects of morphine in the hamster. The lethal dose 50 and the lethal dose 100 are presented.

Morphine sulfate was injected subcutaneously, intramuscularly, and intraperitoneally; the route of administration did not alter the response. In all cases where large quantities had to be given at a single time, a combination of the 3 routes was used. Dosage levels ranged from 1 mg to 2000 mg per kilogram body weight. Normal hamsters of both sexes were included. Body weights were from 26 to 130 g with age corresponding from 1 to 8 months (life span of the hamster usually 12 months). Neither sex, age, nor weight of the animal made any apparent difference in the response to morphine. The seasonal or temperature variations during the course of the investigation also caused no difference in response.

In doses up to and including 150 mg per kg of body weight of the hamster, morphine had no noticeable effect. An increase to 300 mg per kg resulted in stimulation of salivary secretion, some incoordination in the extremities, increased activity, and hyperirritability

to handling or to any direct contact stimulus. At dosage levels of 500 to 600 mg, the animal also showed some discomfort as indicated by circling movements and by the rubbing of its ventral surface on the floor of the cage. This syndrome was different from the Straub reaction² in that there was no arching of the back and the animal was hyperirritable. At this level, convulsions ensued with subsequent recovery. These convulsions, induced by pinching the skin or by blowing the fur, were of the tonic type. Analgesia, as determined by use of heat radiation stimulus, was evident although there was no sedation. As the dose was increased, convulsions became more frequent and severe usually culminating in death. Concurrently, the animal salivated excessively, became damp as if perspiring, and defecated more frequently than normally with semifluid feces. Neither sedation nor narcosis was noted at any time and the respiratory rate was not affected.

By reference to Table I, it will be noted that there were no fatalities in the number of animals used until the dose of 1250 mg per kg body weight was given; this proved to be the L.D. 50 for the hamster. The smallest dose which proved fatal to 100% of the test animals was of the order of 1750 mg per kg; 20 hamsters were included in this group. For only one animal, the guinea pig, has a higher M.L.D. been reported in the literature,³ although Hatcher and Eggleston⁴ have established the M.L.D. for this animal at 400 mg/kg as given by subcutaneous and intramuscular injection and 1000 mg/kg orally.

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¹ Krueger, Hugo, Eddy, Nathan B., and Sumwalt, Margaret, *The Pharmacology of the Opium Alkaloids*, Part 1, pp. 3-76 and 627-758, United States Government Printing Office, Washington, 1941.

² Straub, *Deutsche med. Wchnschr.*, 1911, **37**, 1462, quoted by 1.

³ Gatti, *Ann. d. Ist. Maragliano p. la cura d. tuberc.*, 1913, **7**, 185, quoted by 1.

⁴ Hatcher, R. A., and Eggleston, C., *J. Am. Med. Assn.*, 1914, **63**, 469.

TABLE I.
Toxicity of Morphine Sulfate for the Hamster.

Dose		No. of animals used	No. of survivals	No. of fatalities	Fatality %
Mg/g	Mg/kg				
0.15	150	2	2	0	0
0.30	300	3	3	0	0
0.50	500	6	6	0	0
0.60	600	10	10	0	0
0.90	900	3	3	0	0
1.00	1000	5	5	0	0
1.25*	1250	25	12	13	50
1.50	1500	3	1	2	67
1.60	1600	3	1	2	67
1.70	1700	3	1	2	67
1.75†	1750	20	0	20	100
2.00	2000	3	0	3	100

* The L.D. 50.

† The L.D. 100.

It is quite evident from the above that the hamster is entirely unsuitable for morphine addiction studies. If, by analogy to the dog, the hamster could be addicted to withstand 20 or more times the original lethal dose, it would eventually tolerate around 40 g of morphine per kg body weight per day. On an actual weight basis this would be 4 g for the average adult animal. If given orally, morphine being approximately only one-third as effective by mouth as by injection, would

have to replace the entire food intake of the hamster, which is 6 to 10 g.

Since morphine administration produces in this animal a high degree of analgesia without narcosis or respiratory depression, it may prove to be a desirable one in which to study the mechanism of analgesic action. In addition, it was of interest to note that the action of morphine in stimulating salivary secretion, sweating, and defecation was strikingly similar to that of the parasympathomimetic drugs.

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Hereditary Obesity of Yellow Mice: A Method for the Study of Obesity.*

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In the course of studies on the hereditary obesity of yellow mice first described by Danforth,^{1,2} the following observation was made.

A group of 5 obese females was permitted unlimited amounts of water and Purina dog chow pellets throughout the experiment. Their food intake was measured at 2-6-day intervals, and the caloric intake per mouse per day cal-

culated from a value (3.50 cal./g) obtained by chemical analysis. At varying intervals they were also allowed to drink for a few days one of the following at a time: 10% and 20% solutions of dextrose, 50% sucrose, olive oil, and human plasma with a protein concentration of 17.3%. The unrestricted daily caloric intake per mouse of each of these (excepting olive oil) was calculated. Simultaneously, identical steps were taken with a group of 3 normal albino female mice.

Fig. 1 shows the results. Briefly, none of these substances caused a gain in body weight

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¹ Danforth, C. H., *J. Heredity*, 1927, **18**, 153.

² Rony, H. R., *Obesity and Leanness*, Lea & Febiger, Philadelphia, 1940, 177.