14428

Toxic Levels of Morphine for the Hamster.*

O. Boyd Houchin. (Introduced by Paul W. Smith.)

From the Department of Pharmacology, University of Oklahoma Medical School, Oklahoma City.

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 reaction[2] 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 semi-fluid 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 Eggleston[4] 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.

* Supported by a grant from the Legislature for research in the University of Oklahoma School of Medicine.

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 Mg/g	Dose Mg/kg	No. of animals used	No. of survivals	No. of fatalities	Fatality %
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.

14429 P

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

DAVID A. RYTAND.

From the Department of Medicine, Stanford University School of Medicine, San Francisco.

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 calculated 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

* This work was supported by a grant from the Ella Sachs Plotz Foundation.

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

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

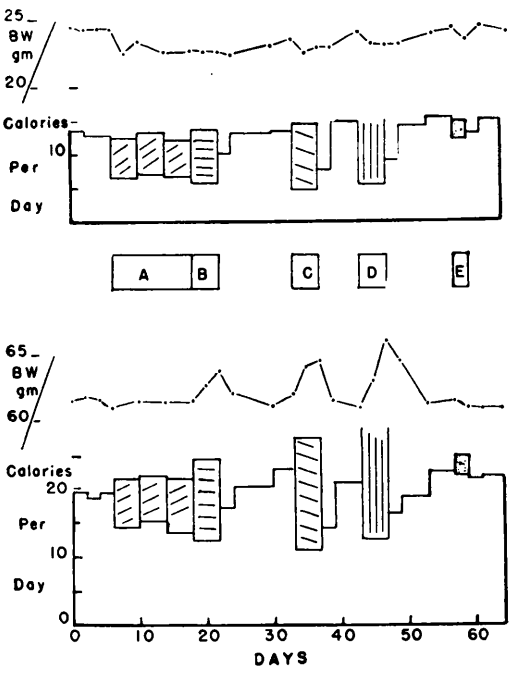

FIG. 1.

Body weight and mean daily caloric intake of 5 obese mice (below) and 3 normal mice (above). Unshaded area, Purina. Shaded area: A, 10% dextrose; B, 20% dextrose; C, 50% sucrose; D, olive oil; E, plasma.

of the normal mice; within the limits of error their caloric intake remained practically constant (see below). But the obese mice gained weight in three 4-day periods: 2.2 g with 20% dextrose, 3.0 g with 50% sucrose, and 4.4 g with olive oil. The caloric intake during 2 of those periods increased by about 12 calories and 24 calories (20% and 50% sugar, respectively), enough to explain most or all of the increased body weight as fat deposition. Moreover, when the sugar or oil was withheld, body weight fell to the original level during a few days in which there was an appropri-

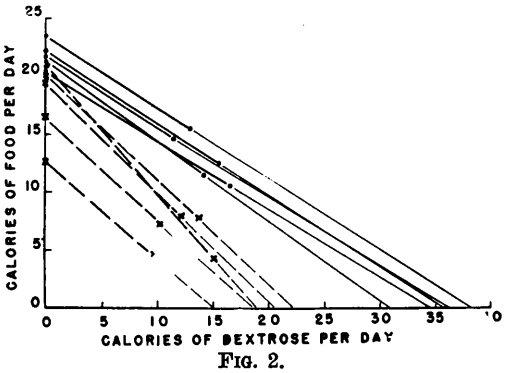

FIG. 2.

Spontaneous substitution of 50% dextrose for Purina. Solid lines, obese female mice; broken lines, normal females. Extrapolations are to emphasize the divergence.

ately reduced caloric intake; surprisingly, under the same conditions, there was also a transient reduction of caloric intake of the normal mice without loss of weight. Dilute (10%) dextrose and plasma protein (17.3%) failed to alter body weight.

Confirmatory observations have been made on 65 mice studied in 20 groups. When "normal" sisters of fat mice are used as controls, some of them gain a gram or two; from this and other evidence (to be published) our present hypothesis is that these animals have "latent" obesity. Excluding such mice, Fig. 2 shows in another manner the results obtained in several groups by the method outlined above, using 50% dextrose, while normal mice substitute 12.2 calories from dextrose for 11.7 calories of their usual diet, the obese substitute 14.1 calories from dextrose for 8.8 calories and so gain in weight.

Among other possible uses of these findings, one seems to have here a method which will permit the study of a fundamental defect of obesity within a short period of time.