

depressed by the narcotic at first, they showed no such effect later. Similar series of daily injections of cobra venom, given the same animals after a period of rest, produced no symptoms of habituation.

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**Behavior of Rats in a Maze in Relation to Analgesic Effect of Cobra Venom and Morphine.**

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An investigation of the effect of repeated injections of cobra venom and morphine on behavior of rats in a circular maze has been described in a previous paper,<sup>1</sup> where it was shown that such administration of morphine effected habituation or tolerance. No habituation, on the contrary, followed injections of cobra venom. Doses of 0.5 mouse unit effected a slight stimulation of the animals' behavior while the primary stimulation produced by larger doses of cobra venom, 1 to 2 mouse units, was followed by a secondary depression, from which the rats recovered the next day. Cobra venom as well as morphine now being used therapeutically for relief of pain, the writer wished to discover whether the analgesia produced by these drugs bore any relation to the general depression in behavior they effect. Eight rats were therefore selected from a series trained in the maze and their running time on 11 successive days was studied after injections of morphine and cobra venom, respectively. Pain threshold was also daily determined before and after administration of each drug. The method employed for studying analgesia has already been described<sup>2</sup> and the various pain thresholds were expressed quantitatively in volts. The results obtained are illustrated by Tables I and II, one showing the effect on running time and pain threshold of rats of successive injections of morphine and the other that of similar treatment with cobra venom. Difference in running time before and after injection of morphine and cobra venom is expressed in seconds and the pain threshold is set forth in volts. Minus signs prefacing figures for running time indicate stimulation or shortening of time of performance after drug's administration, as compared with rats' normal behavior.

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<sup>1</sup> Macht, M. B., *PROC. SOC. EXP. BIOL. AND MED.*, 1939, **42**, 433.

<sup>2</sup> Macht, D. I., and Macht, M. B., *J. Am. Pharm. A.*, 1939, in press.

TABLE I.  
Relation Between the Running Time and Analgesia of Rat After Morphine.

Date (June, '39)	Milligrams of morphine injected	Average difference in running time sec	Difference in pain threshold, volts
12	3	stalled	368
13	3	stalled	430
14	3	60.0	260
15	3	+ 1.6	124
16	3	+ 0.8	89
18	5	60.0	279
19	3	+ 0.2	30
20	3	+ 0.3	32
21	3	- 1.0 (stimulation)	20
22	5	stalled	656
23	5	+ 2.6	172

TABLE II.  
Relation Between Running Time and Analgesia of Rat After Cobra Venom.

Date (June, '39)	Mouse units of cobra venom injected	Average difference in running time, sec	Difference in pain threshold, volts
12	.5	— .2	30
13	.5	— .2	85
14	.5	— .6	45
15	.5	— .3	165
16	.5	— .1	25
18	.5	— .3	85
19	.5	— .6	75
20	.5	— .5	35
21	1.0	— .4	305
22	1.0	— .5	654
23	2.0	60.0	654

It is apparent that the analgesic action of morphine runs parallel to the general depression it effects. Where the morphine injections produced marked general depression of rat, there the greatest degree of analgesia was observed. When the rats had become habituated to the narcotic and their running time was but little impaired, however, the degree of analgesia was very small as indicated by the slight difference in pain thresholds.

In case of cobra venom the findings were radically different, there being no such analogy between general behavior of the rats in the maze and the degree of analgesia produced by the drug. Small doses of cobra venom, 0.5 mouse unit, stimulated activity of the animals and even effected a slight analgesia. Larger doses, 1 mouse unit, of cobra venom did not impair the running time but raised the pain threshold. It was only after a much larger dose of the venom, 2 mouse units or more, that depression of the animals' behavior accompanied a deep analgesia.

Such findings, made throughout the series, agree with clinical

observations reported by various clinicians<sup>3, 4, 5</sup> and throw some light on the mechanism of analgesia produced by cobra venom as compared with that of morphine. The latest work<sup>6</sup> on the physiology of pain seems to point to the hypothalamus as that part of the brain most intimately concerned with sensations of pain. Cobra venom produces analgesia through its direct effect on the hypothalamus or some lower synapse while the action of morphine is not restricted to that region but spreads over the cortical areas, thus depressing the animals' general behavior.

*Summary.* A comparative study of behavior of rats in the maze and the analgesia produced in them by morphine reveals that the two effects run parallel, *i. e.*, the greater the general depression, the greater the analgesia. In case of cobra venom, however, analgesia or heightening of the pain threshold is produced without any marked effect on general behavior of the animals.

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### Sugar Alcohols. XIX. Relationship between Chemical Constitution and Speed of Hemolysis.

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In recent studies<sup>1</sup> concerned with the diuretic action of isomannide (1, 4, 3, 6 dianhydromannitol) it was observed that this compound hemolyzed red cells through osmotic pressure phenomena. This observation prompted the study of the hemolytic activity of a number of sugar alcohols and their anhydrides on the red cells of the dog. The hemolytic activity of certain of these compounds, namely, glycerin, ethylene glycol, erythrol and mannitol has been reported previously by Jacobs.<sup>2</sup>

The apparatus described by Jacobs<sup>3</sup> was employed. The sugar

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<sup>3</sup> Macht, D. I., *Ann. Int. Med.*, 1938, **11**, 1824.

<sup>4</sup> Macht, D. I., *M. Press*, 1939, **201**, 254.

<sup>5</sup> Rutherford, R. N., *New England J. Med.*, 1939, **221**, 403.

<sup>6</sup> Propper-Graghtchenkoff, N. I., *Acta Medica U.S.S.R.*, 1938, **1**, 110.

<sup>1</sup> Krantz, J. C., Jr., and Carr, C. J., *PROC. SOC. EXP. BIOL. AND MED.*, 1938, **39**, 577.

<sup>2</sup> Jacobs, M. H., *J. Cell. and Comp. Physiol.*, 1933-34, **4**, 161.

<sup>3</sup> Jacobs, M. H., and Parpart, A. K., *Biol. Bull.*, 1931, **60**, 95.