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Effect of Repeated Injections of Cobra Venom and Morphine on Behavior of Rats in a Maze.

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Some years ago Macht and Mora found that injections of morphine induced a primary excitation followed by secondary depression in albino rats trained to run in a circular maze.¹ More recently, Macht and Bryan, studying the effects of cobra venom, an analgesic often substituted for morphine, on behavior of rats in Watson's maze, found that small doses of this drug² also excited the animals and that after such primary stimulation, larger doses of the venom produced depression. In the present study the author investigated the respective effects on behavior of rats of *repeated* doses of cobra venom and morphine, injected for long periods, in order to obtain more light on the problem of habituation and other questions connected with continual administration of pain-relieving drugs.

Studies were made on the behavior of 20 male albino rats averaging 225 g in weight. The rats were trained to run in Watson's circular maze until no learning effect was exhibited or until further training resulted in neither a lowering of the running time or reduction in number of errors made. After the optimum learning effect has thus been attained, the time required by each rat to run the maze and the number of errors it made both before and after injection of the drug studied were carefully determined. Before and after receiving the drug each rat was given 5 runs, the first 2 merely to preclude any diurnal learning processes. The time and number of errors made in the last 3 runs were noted and the average performance of each rat per minute was recorded. Daily injections of morphine were given half the series and of cobra venom to the remaining 10 rats for several weeks, at the end of which time the whole series rested for 2 weeks. When the rest period had expired, the procedure was reversed, and injections of morphine were given to the half series that had had cobra venom and of cobra venom to the 10 rats which had received morphine. In this way the comparative effect of both morphine and cobra venom was studied on the same animals. It was found that 0.5 mouse unit of cobra venom either had no effect

¹ Macht, D. I., and Mora, C. F., *J. Pharm. and Exp. Therap.*, 1920, **16**, 219.

² Macht, D. I., *Proc. Nat. Acad. Sc.*, 1936, **22**, 61.

at all or but slightly improved the usual performance of the rats. Larger doses, 2 mouse units or more, of cobra venom effected a primary stimulation succeeded by depression from which, however, the rats fully recovered on the following day. On the other hand, repeated daily injections of 0.5 mouse units or even of 1.0 mouse unit for periods of 2 weeks or more established no habituation as evidenced by the fact that there was no significant change in running performance. Neither was any cumulative effect observed after such a series of injections.

The results obtained with similar injections of morphine were quite different and very interesting. Three milligrams of morphine were found to be the smallest effective dose in the breed of rats studied. When such a dose of the narcotic was injected intraperitoneally, the rats were markedly depressed. When the same dose was administered on succeeding days, however, the rats showed less and less depression until finally no effect was produced by the narcotic or even a slight stimulation was noted. This tolerance varied somewhat with individual rats but in most cases was quickly achieved, a fact which may be explained by the recent finding that morphine is quickly oxidized by the brain tissue of the rat.³ When the morphine dosage was increased to 5 mg, depression was first produced but as injections of this amount continued, the animals acquired a tolerance for this dose also and soon gave in their behavior no evidence of a narcotic effect. Table I is a complete protocol illustrating the findings made throughout the experiments with a rat selected at random from the series tested, and strikingly exhibiting the difference in the animal's behavior after repeated injections of morphine, on the one hand, and (a rest period intervening) after similar treatment with cobra venom, on the other. Similar results were obtained with all the rats in the series. These observations led to the conclusion that repeated injections of morphine induced tolerance or habituation in rats, as indicated by their behavior in a maze, whereas similar treatment with cobra venom had no such effect. These findings are in complete agreement with the clinical observations which numerous physicians have made on adults.^{4, 5} Further data will appear in a more complete paper to be published in the *Journal of Experimental Psychology*.

Summary. Repeated injections of morphine induced in rats running in a circular maze a tolerance or habituation so that although

³ Macht, D. I., and Bryan, H. F., *Compt. rend. Soc. de Urol.*, 1936, **123**, 385.

⁴ Macht, D. I., *Ann. Int. Med.*, 1938, **11**, 1824.

⁵ Macht, D. I., *M. Press*, 1939, **201**, 254.

TABLE I.
Behavior of Rat B After Repeated Injections of Morphine and Cobra Venom, Respectively.

1939	Before administration			Dosage	30 to 45 min. after administration			Wt in g
	Seconds	Avg	Errors		Seconds	Avg	Errors	
4/30	8.1	7.8	6.0	—	—	—	—	210
5/1	8.1	6.5	6.3	—	—	—	—	
5/2	6.0	6.9	8.5	—	—	—	—	
5/3	9.0	7.1	6.0	—	—	—	—	
5/4	5.9	6.4	7.1	—	—	—	—	
5/5	7.0	6.7	6.0	—	—	—	—	
		6.3	6.0	—	—	—	—	212
				Morphine Sulphate				
5/7	8.0	7.0	7.0	3 mg	60.0	60.0	60.0+	
5/8	7.8	7.5	7.0	3 "	16.2	27.1	32.8	
5/9	6.0	6.0	7.0	3 "	9.2	8.8	9.0	
5/10	6.0	5.8	6.0	3 "	6.1	5.8	6.0	
5/11	7.0	6.4	6.1	3 "	6.0	5.8	6.0	
5/12	6.0	5.8	6.2	5 "	stalled	stalled	—	
5/13	5.6	5.8	6.6	5 "	6.2	6.4	6.5	
5/14	6.3	6.0	6.1	5 "	6.4	6.0	6.1	210
5/15	7.2	6.1	6.1	5 "	5.4	5.8	5.7	
5/16	6.9	6.0	6.4	5 "	4.9	5.9	5.6	
5/17	6.2	6.0	6.4	5 "	5.0	5.6	5.6	
5/18	6.0	5.7	6.0	5 "	6.4	6.0	6.1	
5/19	6.0	6.4	6.3	5 "	One hour after administration			
				Cobra Venom.				
6/12	6.4	6.4	6.4	.5 m.u.	6.0	6.1	6.0	210
6/13	6.9	6.8	5.8	.5 "	6.0	5.6	5.9	
6/14	7.1	6.4	6.2	.5 "	6.0	5.6	5.4	
6/15	6.0	6.0	6.0	.5 "	6.0	5.6	5.8	
6/16	6.8	6.0	5.9	.5 "	5.6	5.6	5.8	
6/18	6.0	5.8	5.8	.5 "	5.8	5.8	5.7	
6/19	6.0	6.0	6.1	.5 "	5.2	5.0	5.2	213
6/20	6.1	6.4	5.6	1 "	5.8	5.4	5.5	
6/21	5.8	5.8	5.8	1 "	5.0	5.8	5.4	
6/22	5.9	6.0	5.1	1 "	4.8	5.3	5.1	
6/23	6.0	5.9	6.0	2 "	5.9	5.8	5.9	
					60.0+ 60.0+ 60.0+	two hours later		212

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,¹ 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 described² 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.

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

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