

Summary. Phenylmercuric nitrate in a dilution of 1:100,000 is toxic to suspensions of bakers' yeast as shown by respiration measurements, methylene blue staining, and plating. One per cent of an aqueous-alcoholic yeast extract protects yeast to some extent from this germicidal action. Respiration may cease after introduction of yeast extract and phenylmercuric nitrate, but the yeast is

still viable as shown by methylene blue staining and plating tests. The importance of respiratory depression in the mechanism of phenylmercuric nitrate toxicity is supported, but caution must be exercised in the use of respiratory depression as a sole criterion of toxicity for yeast. The yeast extract overcomes the growth-depressant effects of phenylmercuric nitrate on yeast.

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Comparison of Effects of Cobra Venom and Morphine on Unanesthetized Cat.

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The effect of morphine on cats and other felines differs radically from that which it exerts on man and other higher animals in two respects. (1) Instead of depressing the brain and neuromuscular activity, it produces excitation and delirium. (2) Instead of causing myosis, morphine dilates the pupil. Since cobra venom is employed clinically as an analgesic¹⁻⁴ it was desirable to compare its effects with those of morphine on unanesthetized cats because all previous studies on cats had been made under general anesthesia. In the present paper a comparison was made of (1) behavior and neuromuscular activity and (2) the pupils of unanesthetized cats after administration of the respective drugs.

Twenty cats were employed in this research. Inasmuch as the same animals were used repeatedly after complete recovery from successive injections, over 70 experiments were performed. The cobra venom employed was that made in these laboratories, free from hemotoxic and cytotoxic principles as well as

proteins and virtually a solution of cobra neurotoxin. This solution, assayed on mice, was injected intramuscularly in doses ranging from 5 to 20 m. u. per kilo of cat. Morphine was used in the form of sulfate.

Behavior. While morphine induces in cats an excitement which increases with size of the dose and lasts for 18 hours or more, cobra venom has an exactly opposite action. Doses of 5 to 10 m. u. per kilo of cobra venom had little or no effect on cats. Occasionally they effected a mild euphoria causing the cats to roll pleasurably on their backs in the same way in which they react to catnip. Larger doses of cobra venom (10 to 20 m. u.) were sedative. The animals lay quietly and drowsed but roused to a touch. Very large doses (40 m. u. per kilo) of cobra venom were more depressant and caused unsteadiness of gait and tremor. The behavior of cats injected with cobra venom is apparently the reverse of their reaction to morphine, which induced excitement corresponding to size of the dose. The mild primary stimulation supervening an hour after injection of cobra venom was followed by a sedation proportional to size of the dose and lasting over 18 hours.

Eyes. In all experiments on cat's pupils constant illumination was maintained and there was no abrupt exposure to direct light.

¹ Macht, D. I., *Med. Rec.*, 1941, **153**, 369.

² Chopra, R. N., and Chowhan, J. S., *Ind. Med. Gaz.*, 1940, **75**, 69.

³ Bullrich, R. A., and Ferrari, J. A., *Prensa Medica Argentina*, 1940, **27**, 12.

⁴ Barbeau, A., and Laurendeau, E., *J. de l'Hotel-Dieu de Montreal*, 1940, **9**, 114.

Experiment on Maltese Cat Weighing 2.8 Kilo, 5-14-43

12:00 m., width of pupils about 5 mm; right, ● left, ●
 12:10 p.m., injected 30 m.u. of cobra venom
 12:40 p.m., definite sedation; cat quiet; pupils same width
 2:00 p.m., pupils much narrower, 2 mm. wide; right, ● left, ●
 3:00 p.m., cat somnolent, lying comfortably; pupils very narrow, slit-like, 1 to 2 mm. wide; right, ● left, ●
 Next morning (5-15-43) behavior normal and both pupils, 3 mm., ●

Experiment on Black and White Cat Weighing 2.3 Kilo 5-14-43

12:00 m., pupils 2 to 3 mm. wide; right, ● left, ●
 12:15 p.m., injected 30 mg. of morphine sulphate in muscle
 12:40 p.m., cat very restless and excited; pupils round and maximally dilated; right, ● left, ●
 2:00 p.m., very excited, pupils maximally dilated, do not respond to light
 3:00 p.m., cat restless, excited; pupils still maximally dilated
 Next morning (5-15-43) cat quiet but nervous. Pupils beginning to get smaller; 6 mm. each; right, ● left, ●

Cats injected with morphine invariably revealed mydriasis, even after such small doses as 1 mg per kilo though injection of that amount may not excite. Larger doses of morphine were followed by maximal dilatation of pupils, which did not contract in bright light. The effect of cobra venom was much different. Doses of less than 5 m. u. per kilo did not affect the size of the pupil while larger doses (5 to 20 m. u. per kilo) produced a definite narrowing of the transverse diameter of the cat's eyes, beginning usually an hour after injection of the venom and persisting often till next day. Doses of 20 m. u. per kilo induced marked myosis and slit-like pupils with a transverse diameter of one mm. The respective effects of cobra venom and morphine on cats' behavior and eyes are illustrated by the following protocols and drawings, which do not indicate absolute measurements but only relative sizes of their pupils.

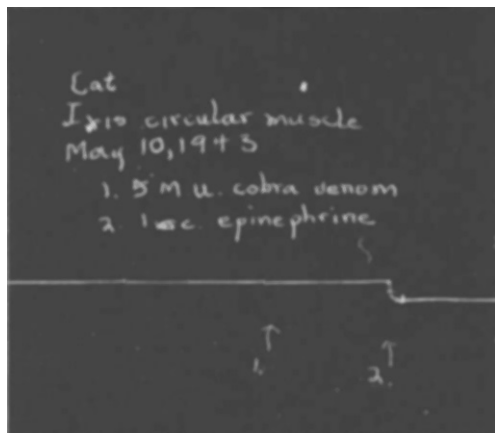


FIG. 1.
Effect of cobra venom and epinephrine on iris muscle.

Sollmann⁵ gives in detail the usual explanation for myosis in *man* after morphine and ascribes it to a stronger constrictor oculomotor tone. The action is central. The

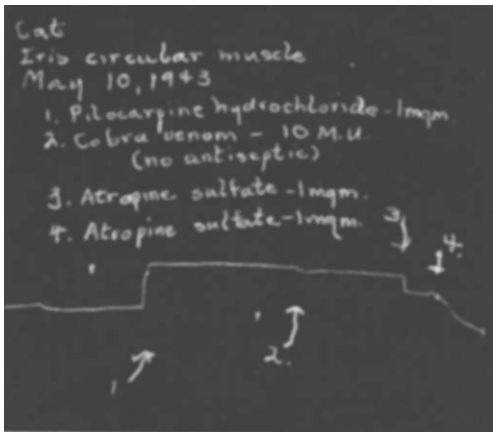


FIG. 2.

Effect of cobra venom and other drugs on iris muscle.

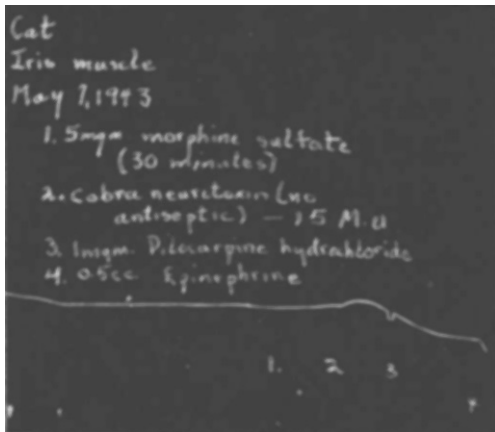


FIG. 3.

Effect of morphine and cobra venom on iris muscle.

oculomotor constrictor center is in a state of partial inhibition through a variety of sensory impulses. When this inhibition is released by such narcotics as morphine, the increase of oculomotor tone produces a myosis.

Local applications of cobra venom to the intact cats' eyes had no effect on the iris. To study the action of cobra venom on the pupil in greater detail the present writer

experimented with the isolated iris muscle of cats *in vitro* by the method first described by Macht^{6,7} and later employed by Poos⁸ and then by Yonkman.⁹ It was found that neither morphine (5 mg in 100 cc of Locke solution) nor cobra venom (10 m. u. in 100 cc of Locke solution) effected any change in tonus of the circular muscle. Larger doses, especially of *crude* cobra venom (1 mg in 100 cc of Locke), slowly relaxed the muscle by its cytotoxic action, yet the muscle still responded to such agents as ergotoxin. The data obtained reveal that the myosis cobra venom effects is not peripheral but central in origin, a finding corroborated by the results of tests which the author made on decerebrated cats with the assistance of Dr. M. B. Macht, neurophysiologist. In these experiments the upper brain was severed just below the thalamus while the oculomotor nuclei were left intact. Postoperative injection of cobra venom in such animals also *narrowed* the pupils.

Summary. 1. In unanesthetized cats morphine induces progressive excitation of the central nervous system and neuromuscular apparatus while cobra venom effects a sedation proportionate to dose of neurotoxin given. 2. While even small doses of morphine produce extreme dilatation of the pupil, cobra venom in small doses has little or no effect on its size though in larger doses it causes a definite myosis. 3. The evidence presented proves that this narrowing of cat's iris is due to a central action of the drug, which heightens the tonus of the oculomotor nucleus.

⁵ Sollmann, T., *Manual of Pharmacology*, Philadelphia, 1942, p. 277.

⁶ Macht, D. I., *Arch. internat. Pharmacodyn. et Thérap.*, 1922, **27**, 175.

⁷ Macht, D. I., Offener Brief, etc., *Arch. f. exp. Path. u. Pharm.*, 1938, **182**, 382.

⁸ Poos, F., *Arch. f. exp. Path. u. Pharm.*, 1927, **126**, 307.

⁹ Yonkman, F., *J. Pharm. and Exp. Therap.*, 1931, **40**, 195.