

Antidotal Action of Picrotoxin in Extreme Cases of Experimental Barbiturate Poisoning.

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About 50 years ago, central stimulants, particularly picrotoxin and coriamyrtin, were used to oppose the depression caused by aliphatic narcotics. Recently, Tatum and his coworkers^{1, 2} tested the antidotal effect of a number of central stimulants with the exception of coriamyrtin in experimental barbiturate poisoning. They produced the poisoning by oral or intraperitoneal administration of the barbiturate and found that picrotoxin was the most effective antidote in both short and long acting barbiturate depressions. Following the barbiturate, picrotoxin was given by diverse routes in doses of 8.8 to 12 mg. per kg. This drug increased the percentage recovery of the animals, *e. g.*, in 7 rabbits given picrotoxin following a dose of 350 mg. of sodium barbital per kg., 4 recovered and 3 died, whereas in 6 controls, 1 recovered and 5 died. Also the average recovery time of the surviving animals was shortened by picrotoxin. However, this dose given by these authors is not in excess of the average fatal dose to any appreciable extent. Gower and van de Erve³ used a larger dose of sodium barbital and injected the drug intravenously. In one dog, they injected 600 mg. of this drug at 3 different times allowing 5 to 9 days to intervene after the complete recovery of the animal from the preceding dose. In these 3 experiments, the amount of picrotoxin which they used over a period of 4 to 8 hours following the sodium barbital injection varied from 6 to 8.8 mg. per kg. The dog recovered in each case within 32 hours. The dose of sodium barbital used by these workers was at least 50% in excess of the average fatal dose and about 3 times the minimum anesthetic dose.

The following experiments were carried out to determine the upper limit of the antidotal efficacy of picrotoxin in acute poisoning produced by a long acting barbiturate, sodium barbital, and by a short acting barbiturate, sodium pentobarbital. In each case, the barbiturate was administered intravenously in divided doses, the

¹ Maloney and Tatum, *J. Pharmacol.*, 1932, **44**, 337.

² Maloney, Fitch and Tatum, *J. Pharmacol.*, 1931, **41**, 465.

³ Gower and van de Erve, *J. Pharmacol.*, 1933, **48**, 141.

first being the minimum anesthetic dose. Then picrotoxin was given in doses sufficient to produce in the animal a state of mild twitchings or convulsions before injecting a subsequent dose of the barbiturate. The time of injection of the total dose of these barbiturates varied from 15 to 52 minutes. After the last dose of the barbiturate, the animal was kept with picrotoxin in a state of hyperexcitability shown by continual twitching or mild convulsions upon gentle sensory stimulation for a period of 12 hours after pentobarbital and about 40 hours after barbital administration. The amount of picrotoxin necessary to maintain this responsiveness decreased as the experiment progressed so the original single doses of 4 mg. of picrotoxin per kg. were gradually reduced to 1 mg. and less per kg. In cases where the respiration or heart failed other measures in addition to picrotoxin such as artificial respiration, strychnine and epinephrine injections, were resorted to in an attempt to save the animal's life but were usually ineffective, or effective only for brief periods. The results of these experiments are summarized in Table I.

TABLE I.
Survival of Animals Poisoned by Massive Intravenous Doses of Barbiturates Following Picrotoxin Treatment.

Animal	Barbiturate*		Total dose injected mg./kg.	Time required for injection min.	Picrotoxin* Total dose injected mg./kg.	Fate of animal†
	Administered					
Dog	Sodium barbital		1000	18	58	Recov. in 48 hr.
"	" "		1250	20	90	" in 72 hr.
"	" "		1250	37	101	" in about 70 hr.
"	" "		1500	15	60	Died in 1 hr. 15 min.
"	" "		1500	20	76	" in 3 hr. 25 min.
"	" "		1650	22	20	" in 1 hr. 30 min.
Dog	Sodium pentobarbital		100	35	18	Recov. in 12 hr.
"	" "		137½	41	76	Died in 11 min.
"	" "		150	38	76	" in 7 min.
"	" "		150	52	58	" in 23 min.
"	" "		160	44	42	" in 22 min.
Rabbit	Sodium pentobarbital		100	15	24	Recov. in 5 hr. 30 min.

*All doses administered intravenously.

†Time after last injection of barbiturate.

This table indicates that dogs receiving 1250 mg. of sodium barbital per kg., which is about 4 times the average fatal dose, will survive with the aid of picrotoxin and this dose of sodium barbital marks approximately the limit of the antidotal power of picrotoxin. With pentobarbital, it is doubtful whether the animal's life can be saved with doses much in excess of 100 mg. per kg. Furthermore,

doses of picrotoxin even as high as 100 mg. per kg., administered during a period of about 24 hours, can be tolerated by the animals if they are in a state of great depression. After recovery, the animals appeared normal in all respects. Thus, the extreme doses of either barbiturates or picrotoxin do not seem to have any deleterious effect upon these animals.

Blood sugar determinations by the Folin-Wu method in 2 animals receiving sodium barbital and picrotoxin showed in one animal no significant change and in the other a marked increase in the blood sugar. The control blood sugar of the first animal receiving 1,000 mg. sodium barbital per kg. was 114 mg. per 100 cc. and varied from 99 to 122 mg. during the first 17 hours after the last dose of the barbiturate, while the blood sugar of the third animal in Table I, in which the control blood sugar was 89 mg. and the dose of the barbiturate higher, rose to a peak of 177 mg. in 4 hours and gradually fell to 138 mg. in 10½ hours. No further determinations were made on either animal. The body temperature was taken at intervals on the latter animal only and was found to be maintained at a remarkably constant level in spite of the depressant action of a large dose of sodium barbital.

The urinary excretion of massive doses of sodium barbital, *i. e.*, 1,000 to 1,250 mg. per kg., is given in Fig. 1. This shows that the kidneys of dogs are capable of excreting large amounts of barbital (calculated as sodium barbital) presented to them, such as 3.857 to 7.397 gm. or 39.7 to 52.8% of the administered dose within the first

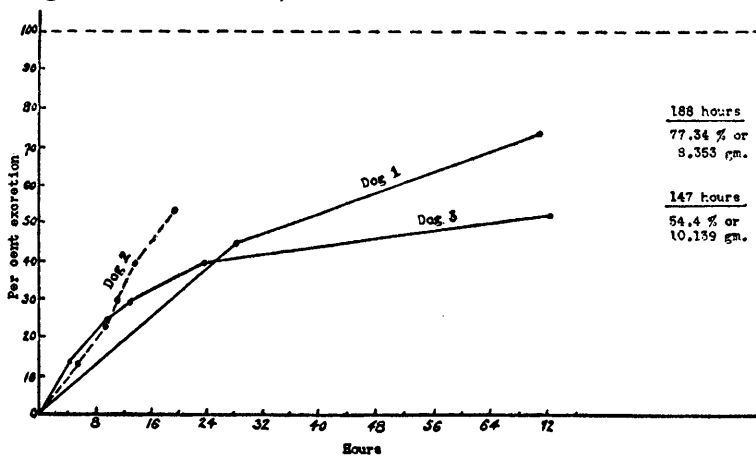


FIG. 1. Excretion of massive intravenous doses of sodium barbital.

Dog 1, wt. 10.8 kg., received 1000 mg. sodium barbital per kg. or 10.8 gm. total; Dog 2, wt. 5.85 kg., received 1250 mg. sodium barbital per kg., or 7.313 gm. total, and Dog 3, wt. 14.9 kg., received 1250 mg. sodium barbital per kg., or 18.625 gm. total.

21 to 28 hours. This is comparable to the excretion of normal nitrogenous constituents as urea and creatinine. Since dogs 1 and 3 in Table I excreted 77.34 and 54.4% respectively of the administered dose up to the time of complete recovery of the animals and negative barbital findings in the blood and urine, it is to be assumed that fairly large amounts of this drug have been destroyed in the body. An indeterminable amount of the urine from dog 2 was lost after the first 21 hours after the administration of the barbiturate and hence the results are not tabulated after that time.

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Carcinoma in the Cottontail Rabbit Following Spontaneous
Virus Papilloma (Shope).

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The Shope rabbit papilloma is an epithelial new growth caused by a filtrable virus¹ and transmissible in series through cottontail (Genus, *Sylvilagus**)¹ and domestic rabbits (Genus, *Oryctolagus*).² Both in the gross and histologically it is similar to the virus papillomata of man, cattle and dogs.^{1, 3-6} Further, it has been found to possess not only the immediate characters of a tumor,⁷ but also the potentiality of progressive alteration until finally it may assume the characteristics of a squamous cell carcinoma with metastases.^{8, 9} We have confirmed these findings.

¹ Shope, R. E., *J. Exp. Med.*, 1933, **58**, 607.

* Two species of cottontail rabbit, *Sylvilagus floridanus malluris* Thomas, and *Sylvilagus floridanus alacer* Bangs have been found suitable for serial transmission of the virus. We have confirmed the latter and can now report successful serial transmission through *Sylvilagus floridanus mearnsi* Allen, native to northwestern New York State.

We wish to thank Mr. George G. Goodwin of the Museum of Natural History, New York City, for the specific allocation of the cottontail rabbits used.

² Shope, R. E., *Proc. Soc. Exp. Biol. and Med.*, 1935, **32**, 830.

³ Ciuffo, G., *Gior. ital. mal. ven.*, 1907, **48**, 12.

⁴ Magalhães, A., *Brazil-med.*, 1920, **34**, 430.

⁵ Findlay, G. M., *Great Britain Med. Research Council*, 1930, **7**, 252.

⁶ De Monbreun, W. A., and Goodpasture, E. W., *Am. J. Path.*, 1932, **8**, 43.

⁷ Rous, Peyton, and Beard, J. W., *J. Exp. Med.*, 1934, **60**, 701.

⁸ Rous, Peyton, and Beard, J. W., *Proc. Soc. Exp. Biol. and Med.*, 1935, **32**, 578.

⁹ Rous, Peyton, and Beard, J. W., *J. Exp. Med.*, 1935, **62**, 523.