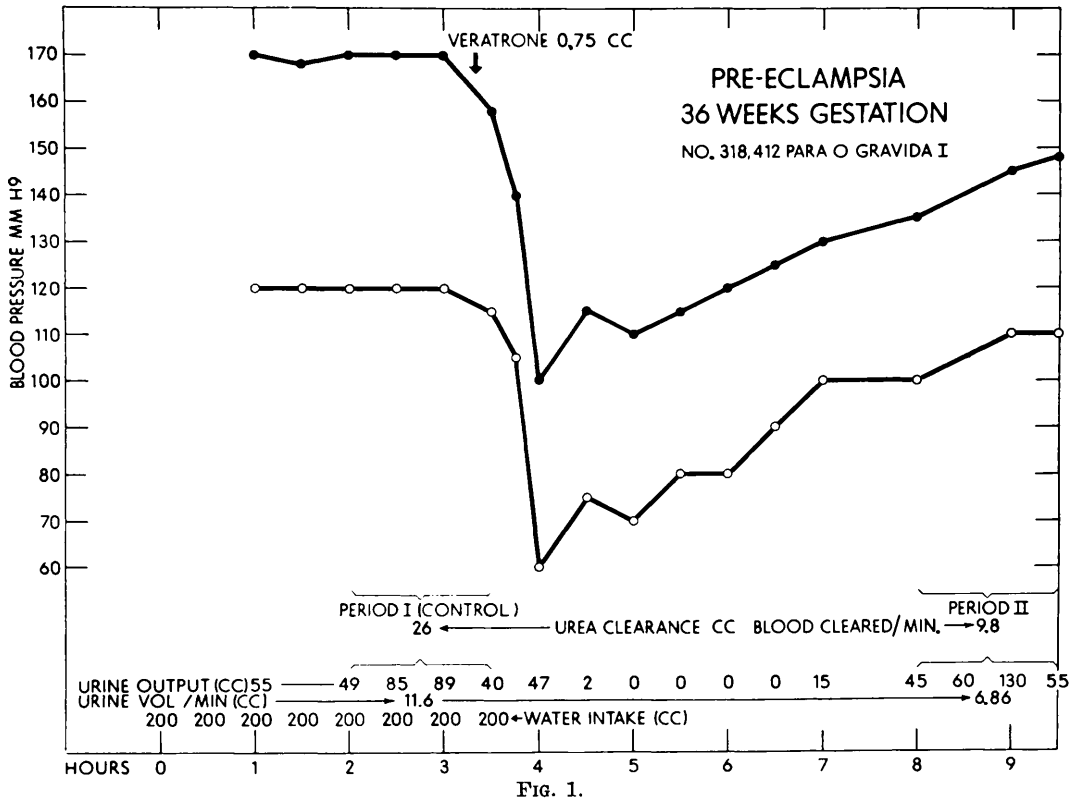


FIG. 1.

emias of pregnancy not only lowers the blood pressure but also decreases kidney function as demonstrated by a depression both in urine volume and urea clearance. It is the opinion of the author that this is the result of two factors: the fall in blood pressure and an alteration in renal dynamics resulting from the action of the drug on the vascular system. Studies on kidney blood flow and glomerular filtration will aid in determining the answer to this problem.

14555

Effect of Xyloquinone in Normal Dogs and Dogs with "Neurogenic Hypertension."

PAUL W. SCHAFER. (Introduced by Lester R. Dragstedt.)

From the Department of Surgery, University of Chicago.

Some evidence supports the view that hypertension observed in experimental renal ischemia is due to faulty deamination of amino acids.[1,2] By the action of decarboxylases pressor amines are formed in the kidney as intermediary products in the metabolism of certain amino acids. In the kidney with a normal blood supply these amines are deaminized to inert substances through the action of the enzyme, amine oxidase. However, in renal ischemia this latter enzyme is not active and

[1] Holtz, P., and Luedtke, K., *Arch. Exp. Path. u. Pharm.*, 1939, **191**, 87.

[2] Bing, R. J., *Am. J. Physiol.*, 1941, **132**, 497.

the pressor amines are not destroyed and may possibly be the basis for the hypertension observed in such conditions. Soloway[3] has shown that certain pressor amines can be inactivated both *in vivo* and *in vitro* by the action of certain quinone precursors, presumably by the formation of amine-inactivating quinones. Following this work Friedman and Soloway[4] demonstrated the marked antipressor effect of 3 paraquinones and one orthoquinone in rats made hypertensive by perinephritic scars. These quinones were effective in lowering blood pressure when given both orally and subcutaneously and were found to produce no change in the blood pressure of normal rats. The exact mode of action of quinones in lowering blood pressure is not known but the most probable theory is that they act through an effect on circulating amines.

Aside from the elevated blood pressure common to both, few points of similarity exist between Goldblatt[5] and "neurogenic"[6] types of hypertension. "Neurogenic" hypertension has been produced in dogs in this laboratory for the past 5 years by Grimson[7] and the author.[8] The procedure has been previously reported and consists essentially of section of carotid sinus and aortic depressor proprioceptor nerves. We have held the view that the elevated blood pressure observed following proprioceptor depressor neurotomy was due primarily to marked increased peripheral vasoconstriction caused by uninhibited action of vasopressor impulses.

Since Friedman and Soloway have demonstrated marked blood pressure reducing properties of certain quinones in rats made hypertensive by renal ischemia we were interested in testing the effect of the most potent of these chemicals on our dogs made hypertensive by a fundamentally different method.

Procedure. Seven adult male dogs were used, 4 with chronic "neurogenic" hypertension and 3 normal controls. The 4 hypertensive dogs had had a sustained elevation of blood pressure for 2, 19, 30, and 32 months respectively with mean arterial blood pressure averages and deviations as follows:

Dog No. 49—Avg, 230 mm Hg; range, 210 to 260 mm Hg.
Dog No. 735—Avg, 235 mm Hg; range, 226 to 240 mm Hg.
Dog No. 139—Avg, 257 mm Hg; range, 220 to 288 mm Hg.
Dog No. 804—Avg, 208 mm Hg; range, 186 to 226 mm Hg.

All 7 dogs were given a subcutaneous injection of 10 cc of a 0.1% solution of 2,5-dimethyl paraquinone (xyloquinone) in sterile normal saline solution per kg of body weight. Mean femoral arterial blood pressure determinations were made at intervals as indicated in Table I. After the 4 hypertensive animals had recovered from the effect of the xyloquinone injection they were each given a subcutaneous injection of 10 cc of a sterile normal saline solution per kg of body weight and blood pressure determinations made at intervals as indicated in Table I. The average blood pressure changes for each group are plotted in Fig. 1.

Results. No significant changes were observed in the mean arterial blood pressure of normal dogs injected with xyloquinone or in hypertensive dogs injected with normal saline solution in the amount indicated above. Hypertensive dogs given a single subcutaneous injection of 10 mg of xyloquinone per kg of body weight were observed to have a precipitous reduction of blood pressure by 120 mm Hg., maximal at 6 hrs, and requiring 4 days for complete recovery. No changes could be detected in the behavior of any of these animals and the local sites of injection did not show signs of inflammation. Body temperature and weight remained normal. Smaller amounts of xyloquinone than that indicated above have been used with less marked and less prolonged effect. Larger amounts, given deliberately to produce signs of overdosage,

3 Soloway, S., and Oster, K. A., PROC. SOC. EXP. BIOL. AND MED., 1942, **50**, 108.

4 Friedman, B., and Soloway, S., PROC. SOC. EXP. BIOL. AND MED., 1942, **51**, 195.

5 Goldblatt, H., Lynch, J., *et al.*, *Am. J. Path.*, 1933, **9**, 1942.

6 Heymans, C., and Bouchaert, J. L., *C. R. Soc. de biol.*, 1931, **106**, 471.

7 Grimson, K. S., *Arch. Surg.*, 1941, **43**, 284.

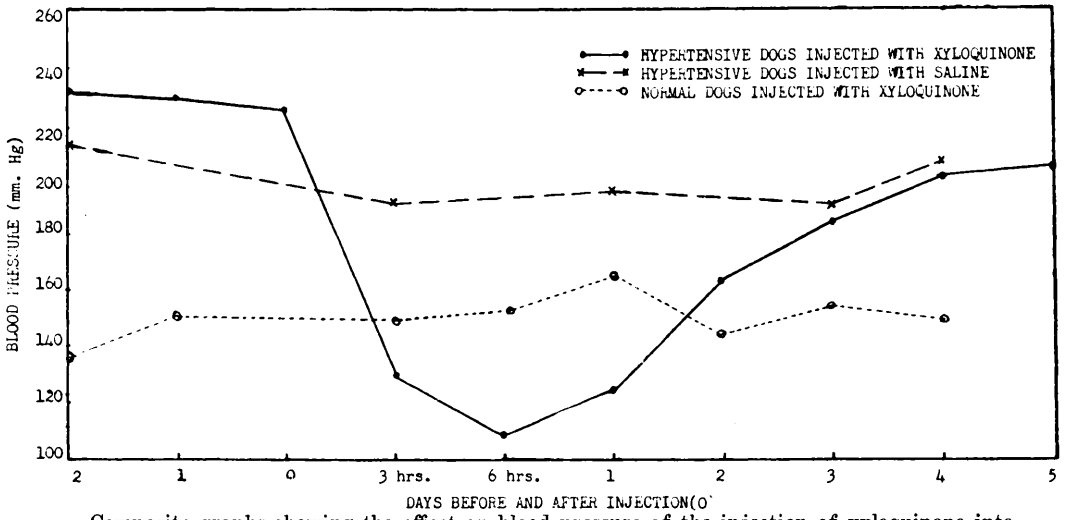
8 Schafer, P. W., PROC. SOC. EXP. BIOL. AND MED., 1942, **49**, 327.

TABLE I.

Blood Pressure Readings Before and After Injection of Xyloquinone in Normal Saline Solution into Four Hypertensive Dogs (Group I), and into Three Normal Dogs (Group III). Blood Pressure Readings Before and After the Injection of an Equal Volume of Normal Saline into Three Hypertensive Dogs (Group II) Are Also Shown.

	Blood pressure (mm Hg) on days before and after injection										
Dog No.	2	1	0	3 hrs	6 hrs	1	2	3	4	5	6
Group I—Hypertensive Dogs Injected with Xyloquinone (10 cc .1% sol./kg body weight).											
49		240	220	120	100	144	170	190		240	230
735		226		106	90	80	176	206		170	200
139		210	220	128	130	156	174	198		180	200
804		226	200	170	122	126	140	146		216	186
Group II—Hypertensive Dogs Injected with Normal Saline (10 cc/kg body weight).											
49	260			230		240		230	250		
735	188			160		140		188	180		
139	192			186		210		152	190		
Group III—Normal Dogs Injected with Xyloquinone (10 cc .1% sol./kg body weight).											
296	140	165		160	170	200	160	160	166		
297	130	140		140	150	140	132	136	126		
298	140	150		150	150	160	146	170	160		

FIG. 1 - EFFECT OF XYLOQUINONE ON THE BLOOD PRESSURE OF HYPERTENSIVE AND NORMAL DOGS.



Composite graphs showing the effect on blood pressure of the injection of xyloquinone into hypertensive dogs (Group I) indicated by the solid line, and into normal dogs (Group III) indicated by the dotted line. The effect of injection of saline solution into hypertensive dogs Group II) is indicated by the dashed line.

have been found to cause marked intravascular hemolysis, hemoglobin cast occlusion of renal tubules, uremia and death.

Discussion. Since xyloquinone is effective in lowering the blood pressure of rats made hypertensive by renal ischemia and dogs made hypertensive by proprioceptor depressor neurotomy one has to ascribe to it either a non-specific depressor action or else consider the possibility that both types of hypertension may have similar humoral aspects. The fact that the blood pressure of normal rats and normal dogs is not changed by this chemical and that the animals present no untoward signs or symptoms make it seem unlikely that the effect is non-specific. Of obvious interest would be the effect of this agent on the blood pressure of patients with "essential hypertension" but the hazard of hemolytic reactions should cause this problem to be approached with due care.

Summary. 1. 2,5-dimethyl paraquinone was

found to cause a marked reduction in the blood pressure of dogs made hypertensive by proprioceptor depressor neurotomy. 2. No significant changes were observed in the blood pressure of normal dogs given an amount of this chemical sufficient to cause a marked effect in hypertensive dogs.

The author wishes to acknowledge the technical assistance of Carl Laestar.

14556

Ineffectiveness of Sodium Succinate in Control of Duration of Barbiturate Anesthesia

HENRY A. LARDY, R. GAURTH HANSEN, AND PAUL H. PHILLIPS.

From the Department of Biochemistry, College of Agriculture, University of Wisconsin, Madison.

Recently Soskin and Taubenhaus[1] have reported the effectiveness of sodium succinate in shortening the duration of barbiturate anesthesia in rats. Succinate was also reported to be of some benefit as an antidote for lethal doses of pentobarbital. The impetus for their experimental work was the observation of Quastel and Wheatley[2] that barbiturates depress the respiration of brain tissue *in vitro* when glucose, pyruvate, or lactate are the substrates, but that succinate oxidation is not inhibited. We had found[3] that in tissue preparations which rapidly oxidized succinate *in vitro* the oxidation was not coupled with phosphorylation. Coupling of oxidation with phosphorylation is, as far as is known. the only mechanism by which the organism may derive energy from the oxidation of metabolites. While we have no reason to doubt that succinate oxidation *in vivo* is coupled with phosphorylation the results with tissue preparations suggested that the alterations in tissue during the preparation for manometric experiments are such that the rate of oxidation of substrates *in vitro* does not necessarily indicate the relative importance of that substrate as an energy source *in vivo*.

The observations of Soskin and Taubenhaus seemed of sufficient importance to merit further investigation. Upon repetition of their work we were unable to confirm their conclusion that the administration of sodium succinate shortens the duration of both pentobarbital and amytal anesthesia in rats.

Experimental and Results. Male rats of the Sprague-Dawley strain, weighing from 200 to 250 g and maintained on stock rations, were the experimental subjects. The sodium salts of the barbiturates in aqueous solution were injected intraperitoneally. Where succinate was administered it was injected as an aqueous solution containing 200 mg of sodium succinate per cc. Equivalent amounts of malate were given some animals. Both succinate and malate were injected 1 to 5 minutes after the barbiturate. Duration of anesthesia was measured from the time of disappearance of the eyelid reflex until the animal arose and moved about the cage. Other experimental conditions and the results obtained are shown in Table I.

In Experiment 1 neither succinate nor malate, administered intramuscularly following the intraperitoneal injection of pentobarbital, significantly affected the duration of anesthesia. Similar results were obtained in Experiment 2 with pentobarbital and in Experiment 3 with amytal.* The experimental conditions in these experiments were very similar to those under which Soskin and Taubenhaus obtained the most dramatic

1 Soskin, S., and Taubenhaus, M., *J. Pharm.*, 1943, **78**, 49.

2 Quastel, J. H., and Wheatley, A. H. M., *Proc. Roy. Soc. London*, 1932, **B112**, 60.

3 Boyer, P. D., Lardy, H. A., and Phillips, P. H., unpublished data.

* We are indebted to Dr. O. S. Orth for supplying the amytal used in these experiments.