cerebellum, occurring in young rats of mothers reared on a diet containing a high percentage of cystine and deficient in choline, are described and briefly compared to the brain hemorrhages observed in other vitamin deficiencies.

13893

Quinones as Blood Pressure Reducing Agents in Hypertensive Rats.*

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Introduction. Following the work of Holtz,[1] Bing and his co-workers[2,3] have demonstrated that experimental renal hypertension can be produced by the injection of amino acids into the ischemic kidney of cats. This work has provided a basis for the hypothesis that the hypertension resulting from an interference with the blood supply to the kidney may be due to faulty deamination of certain amino acids. This process is catalyzed by amine oxidase and requires the presence of oxygen. Under anaerobic conditions, however, such as may exist in renal ischemia, decarboxylation without subsequent deamination would occur, thus leading to the formation of pressor amines. An accumulation of these substances would tend to elevate the blood pressure.

It has been shown that certain pressor amines can be inactivated by quinone precursors.[4,5] The present study deals with the effect of certain quinones on the blood pressure of rats with experimental renal hypertension.†

Method. Young male rats weighing 150-200 g were used. Hypertension was produced by wrapping one or both kidneys in cellophane.[6] Blood pressures were recorded in the tail using the method of Williams, Harrison and Grollman.[7] The systolic blood pressures of over 600 normal rats tested by this method in our laboratory ranged between 100 and 140 mm of mercury. The blood pressure of hypertensive rats was generally 40 to 80 mm of mercury above the preoperative level. Rats were considered suitable for testing when the blood pressure level had been elevated and stable for a period of at least one month. Daily readings were made for one week prior to, during and immediately following administration of the agent to be tested. Nine compounds were tested by the subcutaneous and 5 by the oral route. When used orally a weighed sample of the compound was mixed daily with a submaximal quantity of the food which the animal had been accustomed to consume. Thus the daily dosage in feeding experiments was approximate and not exact. Quinones which proved effective in reducing the blood pressure in hypertensive animals were tested also on rats with normal blood pressure.

Results. Four of the 10 compounds tested were effective in lowering the blood pressure of hypertensive rats. As will be seen in

* Several of the compounds used in this work were secured through the courtesy of the Wallerstein Laboratories, to whom we are deeply indebted.

1 Holtz, P., Heise, R., and Luedtke, K., *Arch. Exp. Path. u. Pharm.*, 1938, **191**, 87.

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

3 Bing, R. J., and Zucker, M. B., *J. Exp. Med.*, 1941, **74**, 235.

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

5 Oster, K. A., *Nature*, 1942, **150**, 289.

† Similar experiments on hypertensive dogs are being conducted.

6 Friedman, B., Jarman, J., and Klemperer, P., *Am. J. Med. Sc.*, 1941, **202**, 20; Page, I. H., *Science*, 1939, **89**, 273.

7 Williams, J. R., Jr., Harrison, T. R., and Grollman, A. J., *J. Clin. Invest.*, 1939, **18**, 373.

TABLE I.
Effect of Various Quinones on the Blood Pressure of Hypertensive Rats.

Quinone tested	Method of administration	Medium	Effect	No. of rats used	Avg initial B.P. level Mm Hg	During administration: Avg lowest B.P. Mm Hg	During administration: Avg max. change Mm Hg	Avg No. of days before change	Daily dose mg
2,5 Dimethyl paraquinone*	subc.	saline	anti-pressor	8	191	124	67	3	1-2
2,5 " "	"	oil	"	4	186	130	56	5	1-4
2,5 " "	oral	food	"	6	186	121	65	7	25-100
2 Methyl 5 isopropyl paraquinone†	subc.	saline	"	12	188	135	53	2	2-10
2 " 5 " "	"	oil	"	29	185	130	55	5	10-40
2 " 5 " "	oral	food	"	13	191	136	55	4	100-200
2 " 5 " "	"	oil	"	15	185	135	50	4	8-50
Sodium rhodizonate	subc.	saline	"	12	190	129	61	3	6-12
Trimethyl paraquinone	"	"	"	12	188	136	52	3	2-8
Triquinoyl	"	"	0	6	186	161	25	—	10-30
4,5 Dimethyl orthoquinone	"	"	0	12	194	180	14	—	5
2,5 Dihydroxy paraquinone	"	"	0	4	206	180	26	—	5
2,5 Dimethyoxy paraquinone	oral	food	0	4	220	206	14	—	154
Sodium chloranilate	subc.	saline	0	4	177	169	8	—	2
" "	oral	food	0	4	176	171	5	—	175
β-Hydroxy 1,4 naphthaquinone	subc.	saline	0	4	203	189	14	—	2
β " 1,4 "	oral	food	0	4	202	192	10	—	470

*Xyloquinone.
†Thymoquinone.
Subc. = subcutaneous.

Table I, the 4 effective substances were (1) 2,5 dimethyl paraquinone (Xyloquinone), (2) 2 methyl 5 isopropyl paraquinone (Thymoquinone), (3) sodium rhodizonate and (4) trimethyl paraquinone. In most cases in which a depressor effect was obtained, the blood pressure of the hypertensive rats was reduced to the normal range and on discontinuing the administration of the compound the hypertension returned, but usually not quite to the previous hypertensive level. This depressor effect could be produced repeatedly on the same animal, the blood pressure returning to a high level each time after discontinuing the medication. The 6 other compounds tested were ineffective in reducing the blood pressures by amounts which we regarded as significant.

Table I summarizes the results of experiments on over 100 rats, many of which were used in more than one experiment. It will be seen that only such substances were considered anti-pressor as produced (1) a fall to at least 150 mm of mercury, and (2) an average maximum drop of at least 30 mm.

Fig. 1 illustrates typical averaged results with one of the effective compounds, xyloquinone, injected subcutaneously.

It is noteworthy that the 4 effective compounds did not influence the blood pressure of normal non-hypertensive rats.

One of the effective compounds, trimethyl paraquinone, sometimes gave toxic symptoms (methemoglobinemia), so that further ex-

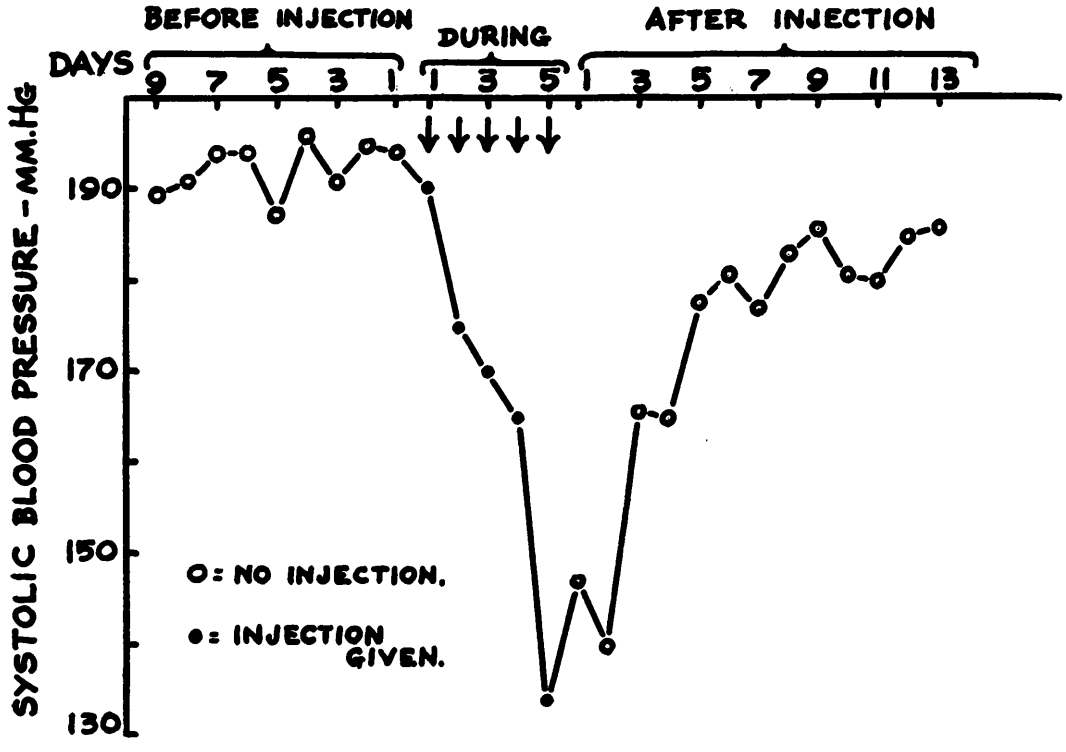

FIG. 1.
Anti-pressor effect of subcutaneous injection of xyloquinone in saline. Results represent averaged blood pressures of 4 rats. Dosages were from 1-4 mg for 5 successive days.

periments with this substance were discontinued. In the case of one ineffective substance, β-hydroxy 1,4 naphthaquinone, oral administration of even such a huge dose as 470 mg daily for 4 days produced no effect on the hypertension, but produced orange pigmentation of the skin and mucosa of the rats.

In several of the experiments the temperature of the rats was measured before and during the administration of quinones, and in none was there a significant change in temperature. In several instances, however, with large doses of quinones, death occurred preceded by rapid decline in blood pressure.

When the compounds xyloquinone or thymoquinone were administered with ground-up rat food, the rats lost weight and the blood pressures fell, but control experiments convinced us that the drop in blood pressure was not associated with the loss of weight as such, but was due to the compounds administered. The solubility of the preparations of quinones used was of varying degree, and so some had to be injected as suspensions.

Experiments were performed to determine the stability in oil of one of the effective compounds, *i.e.*, thymoquinone. After solution in olive oil it was allowed to stand in the refrigerator for 6 weeks; on being then tested experimentally the solution was as effective as it had been originally. Chemically, the effective compounds are stable if kept in dry containers in the dark.

Discussion of Results. Three of the 4 effective compounds (xyloquinone, thymoquinone and trimethylquinone) are paraquinones, while the fourth (sodium rhodizonate) is a diorthoquinone. The paraquinones in general have the advantage of greater stability in saline solution and thus are to be preferred to the orthoquinones.

It is not clear at the present time just why some of the quinones are effective while others are not. Too few compounds have been tested to permit correlation of anti-

pressor properties with chemical structure. The mechanism of action of the quinones is not clear. The inactivation or destruction of pressor amines may conceivably take place by conjugation, by formation of Schiff bases or by acting as catalysts for oxidative deamination.

Great caution must be employed in evaluating changes in blood pressure resulting from therapeutic agents administered parenterally. Striking reductions in blood pressure have been reported in man and in experimental animals following the use of a variety of non-specific measures such as the administration of pyrogens,[8] inactivated tyrosinase,[9] and implantation of foreign protein.[10] All of these reactions are associated with fever or local inflammatory changes. In this study slight local reactions occurred with some, but not with all of the effective quinones used. Equally severe local inflammatory reactions were observed with most of the other non-effective quinones. Febrile reactions were not observed. Moreover, the preparations were effective when used by mouth so that the effect cannot be attributed to a non-specific pyrogenic action.

The fact that the blood pressure of normal non-hypertensive rats is not affected by potent anti-pressor quinones, suggests that their action is not that of a general vasodilator.

Summary. 1. Three paraquinones and one diorthoquinone were found to have well-defined blood pressure reducing properties in hypertensive rats. These compounds are 2,5 dimethyl paraquinone (xyloquinone), 2 methyl 5 isopropyl paraquinone (thymoquinone), trimethyl paraquinone and sodium rhodizonate. 2. This depressor effect is not associated with a febrile reaction and can be elicited by the oral as well as the subcutaneous route of administration. 3. These compounds have no effect on the blood pressure of normal non-hypertensive rats.

[8] Chasis, H., Goldring, W., and Smith, Homer W., *J. Clin. Invest.*, 1942, **21**, 369.

[9] Prinzmetal, M., Alles, G. A., Margolis, C., Kaylend, S., and Davis, D. S., PROC. SOC. EXP. BIOL. AND MED., 1942, **50**, 288.

[10] Friedman, Ben, Jarman, J., and Marrus, J., *J. of the Mt. Sinai Hosp.*, 1942, **8**, 534.