TABLE II.
Concentration of PAB in the Blood of Mice Following the Administration of Various Dosages of PAB.

Dose per kg	Time after admin., hr	PAB in blood	Avg
1 g i.p.	2	107, 131, 221, 113, 120	138
2 g i.p.	1½	446, 453, 382, 442,	431
1 g oral	1½	127, 125, 121, 110, 159	128

in the blood (Table II) indicate that a high concentration of PAB was present when the arsenical was injected. Even larger doses of PAB have been injected intraperitoneally (3g/kg), but also without the production of significant antagonism of Mapharsen toxicity; at this dosage level PAB caused occasional delayed deaths and higher doses could not be employed.

The data presented in Table I indicate that Orthoform exerts no protective action against Mapharsen toxicity. An explanation for the higher mortality rate with Orthoform in one experiment is not apparent. When Orthoform was given intravenously as a solution of the hydrochloride (pH 2.8) (175 mg/kg), prior to Mapharsen, 10 of 21 mice died (48%), while 15 of 26 (54%) which received dilute hydrochloric acid of the same pH, prior to Mapharsen, died without a significant difference in the survival time of the 2 groups.

Summary. No significant reduction in the acutely fatal toxicity of *m*-amino-*p*-hydroxyphenylarsenoxide (Mapharsen) in mice was produced by the prior administration of sodium *p*-aminobenzoate or the methyl ester of *m*-amino-*p*-hydroxybenzoic acid (Orthoform) under the conditions employed.

Grateful acknowledgment is made to Miss Helen Morrison for technical assistance, and to Miss Ethol Shiels and Miss Elizabeth Patch for the determination of PAB concentrations in blood.

14226

Treatment of Experimental Renal Hypertension With Vitamin A Concentrates.*

G. E. WAKERLIN AND W. G. MOSS.

From the Department of Physiology, Chicago Colleges of the University of Illinois.

Subsequent to Govea-Peña and Villaverde's[1,2] favorable results in the treatment of essential hypertension in man with large doses of vitamin A orally, we obtained significant reductions in the blood pressures of renal hypertensive dogs with a vitamin A concentrate.[3] In our preliminary report, however, we indicated our intention of investigating the possibility that the observed therapeutic effect of the concentrate was due to some unknown constituent of the concentrate other than vitamin A. We now report our results to date with vitamin A concentrates in experimental renal hypertension.

Methods. Seven dogs were rendered hypertensive by the Goldblatt technique and the resulting hypertension was permitted to stabilize over a period of 5 to 8 months. Mean blood pressure readings were obtained by puncture of a femoral artery 2 to 3 times a week. Studies on the blood urea nitrogen, urinalyses, and determinations of body

* Aided by a grant from the Winthrop Chemical Company, New York City.

1 Govea-Peña, J. and Villaverde, M., *Rev. Cubana Cardiol.*, 1940, **2**, 332.

2 Villaverde, M., and Govea-Peña, J., *Bol. de la Aso. Med. de P. R.*, 1941, **33**, 238.

3 Wakerlin, G. E., Moss, W. G., and Smith, E. L., *Science*, 1942, **96**, 161.

weight were made at monthly or bi-monthly intervals. Three dogs were treated daily with 200,000 units of Lot 1 of a vitamin A concentrate† dissolved in 1 cc of sesame oil by mouth for 3 months, followed by 400,000 units of the concentrate in 2 cc of sesame oil for an additional 3 months. These dogs have been observed for 6 to 9 months since treatment was stopped. One dog was given a daily dose of 400,000 units of a highly purified vitamin A alcohol in 2 cc of sesame oil orally for 3½ months, and after a rest period of 2 months, 400,000 units of Lot 2 of the vitamin A concentrate in sesame oil daily for 1½ months, followed by the same dosage of Lot 3 of the concentrate in fish liver oil for 1½ months. One dog received 2 cc of Lot 4 of the concentrate in fish liver oil subsequent to heat inactivation of the vitamin A in the presence of oxygen, daily by mouth for 3½ months, followed by a rest period of 2 months and then by 400,000 units of Lot 2 of the concentrate for 1½ months and the same dosage of Lot 3 of the concentrate for 1½ months. The remaining 2 dogs were given oral daily doses of 1 cc of sesame oil for 3 months, followed by 2 cc of sesame oil for another 3 months. One of these 2 animals has been observed for 7 months subsequent to sesame oil administration. The other, after a rest period of 4 months, received 400,000 units daily of Lot 2 of the concentrate for 1½ months and the same dosage of Lot 3 for 1½ months.

In addition to the therapeutic experiments and in view of the prophylactic effect of certain renal extracts in experimental renal hypertension,[4,5] 6 dogs were given 400,000 units of Lot 2 of the vitamin A concentrate daily by mouth for 3 months before and 3 months after constriction of the renal arteries in order to test the possible prophylactic effect of the concentrate. Five control dogs were given oral daily doses of 2 cc of sesame oil for 3 months before and 3 months after constriction of the renal arteries. Otherwise these animals were subjected to the same observations as the dogs on the therapeutic experiments.

Blood serum vitamin A and carotene determinations were made on the dogs at intervals of 2 to 4 weeks by the Carr-Price method as modified by McCoord and Luce-Clausen.[6]

Results. I. *Therapeutic Experiments.* Striking reductions in blood pressure were observed in each of the 3 dogs given Lot 1 of the vitamin A concentrate. The results for one of the dogs which are typical for the other 2 animals are illustrated in Fig. 1. The blood pressures of this dog were reduced from a hypertensive range of 190-210 mm Hg. to the preconstriction normotensive level of 130-140 mm Hg. Since treatment was stopped 6 months ago, the blood pressures have shown a gradual increase to 160-180 mm Hg. In each dog there was a significant decrease in blood pressure during the third and fourth weeks of treatment with a more gradual fall during the following 5 months of therapy.

The dog given the purified vitamin A and later Lots 2 and 3 of the concentrate showed no significant change in its hypertensive level during or subsequent to treatment. This was likewise true for the dog receiving the heat-inactivated vitamin A concentrate and later Lots 2 and 3, and also for the 2 dogs given sesame oil, including the one subsequently given Lots 2 and 3 of the concentrate.

II. *Prophylactic Experiments.* Three of the vitamin A concentrate dogs and 2 of the sesame oil dogs developed typical experimental hypertension following moderate constriction of the renal arteries. The remaining 3 concentrate dogs and 3 sesame oil dogs developed malignant hypertension terminating fatally in one week or less subsequent to severe constriction of the renal arteries.

III. *Vitamin A Determinations.* Serum vitamin A determinations on the dogs not receiving vitamin A showed values of 25-270

† The vitamin A concentrates and other preparations studied were supplied through the courtesy of the Department of Medical Research, Winthrop Chemical Company, New York City.

4 Wakerlin, G. E., Johnson, C. A., Smith, E. L., Moss, W. G., and Weir, J. R., *Am. J. Physiol.*, 1942, **137**, 515.

5 Goldblatt, H., *J. A. M. A.*, 1943, **122**, 136.

6 McCoord, A. B., and Luce-Clausen, E. M., *J. Nutrition*, 1934, **7**, 557.

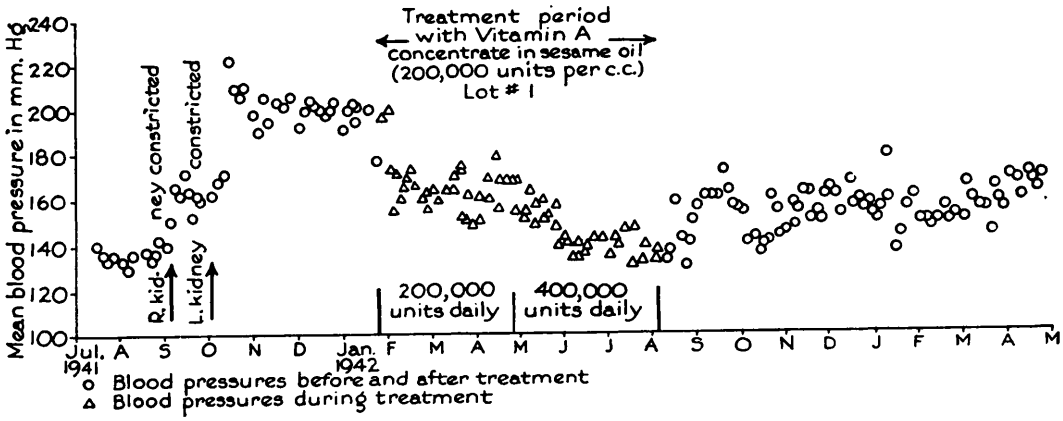

FIG. 1.

γ/100 cc. During vitamin A administration, the determinations varied between extremes of 250 and 8300 γ/100 cc. The variations in any single dog, however, were less pronounced. During the months following vitamin A administration the serum values have decreased but slightly. The carotene values varied from 0 to a trace.

IV. *Absence of Toxic Effects.* No toxic effects were detected in any of the animals. The appetites of the dogs remained excellent, their weights constant, and their blood urea nitrogens and urines normal. The two dosages of vitamin A used were somewhat less than 1/20 and 1/10 of the amounts reported toxic for rats by some workers[7,8,9] but less than 1/100 and 1/50 of the toxic levels reported by others[10,11] who contend that the lower values of the former investigators are due to impurities.

Discussion. The group of 3 hypertensive dogs treated with Lot 1 of the vitamin A concentrate is admittedly small but the antihypertensive effect in each animal was striking. We have never seen spontaneous blood pressure decreases similar to the reductions observed in these 3 dogs in 100 renal hypertensive animals during the past 3 years. Nor did a number of reputedly antihypertensive agents studied by one of us lower the blood pressures of renal hypertensive dogs.[12]

Obviously the antihypertensive effect of Lot 1 of the concentrate was not due to vitamin A inasmuch as Lots 2 and 3 and the purified vitamin A alcohol were inactive antihypertensively. Moreover, Katz and his coworkers obtained no antihypertensive effects in renal hypertensive dogs from a different vitamin A concentrate[13] or from Lot 2 of the concentrate studied by us.[14] Likewise, Geiger[15] found no significant blood pressure change in one hypertensive dog given still another type of vitamin A concentrate. Inasmuch as Lot 4 of the concentrate was not tested for antihypertensive activity prior to heating, no conclusions can be drawn from the negative results with the heat-inactivated vitamin A concentrate. Before we determined that Lots 2 and 3 were without antihypertensive effect, we had interpreted this result as suggesting that the antihypertensive activity of Lot 1 would be destroyed by heating in the presence of oxygen.

Since Lot 2 of the concentrate subsequently proved to be without therapeutic antihypertensive effect, its failure to have any prophy-

7 Domagk, G., and von Bobeneck, P., *Virch. Arch. f. Path. Anat.*, 1933, **290**, 385.

8 von Drigalski, W., *Klin. Woch.*, 1933, **12**, 308.

9 Popper, H., and Brenner, S., *J. Nutrition*, 1942, **23**, 431.

10 Vedder, E. B., and Rosenberg, C., *J. Nutrition*, 1938, **16**, 57.

11 Ikegaki, I., *Ztschr. f. Vitaminforsch.*, 1938, **7**, 113.

12 Wakerlin, G. E., and Gaines, W., *Am. J. Physiol.*, 1940, **130**, 568.

13 Katz, L. N., *J. A. M. A.*, 1943, **122**, 60.

14 Katz, L. N., personal communication.

15 Geiger, E., personal communication.

lactic effect is not surprising.

At present we have no explanation for the marked difference in the results obtained with Lot 1 and Lots 2 and 3 which presumably were prepared by the same method. Possibly some unrecognized variation in the method of preparation led to the production of the unknown antihypertensive constituent in Lot 1. Unfortunately further studies with Lot 1 can not be conducted since the supply is exhausted.

The relationship of the antihypertensive substance in Lot 1 to that reported by Grollman and Harrison[16] in fish liver oils is, of course, problematical. The vitamin A concentrate which they reported as showing some therapeutic effect in hypertensive rats was the same as Lot 2 which proved inactive in our hypertensive dogs.

We are of the opinion that an exhaustive search for the antihypertensive agent of Lot 1 is well-warranted, since it was effective by mouth and apparently in small amounts.

This report should discourage the use of vitamin A concentrates in the treatment of human hypertension, unfortunately stimulated by our preliminary report.

[16] Grollman, A., and Harrison, T. R., PROC. SOC. EXP. BIOL. AND MED., 1943, **52**, 162.

Conclusions. 1. One lot of a vitamin A concentrate dissolved in sesame oil produced striking reductions in the blood pressures of renal hypertensive dogs when administered by mouth in a dosage of 200,000 units daily for 3 months followed by 400,000 units daily for 3 months.

2. Second and third lots of the concentrate dissolved in sesame oil and fish liver oil respectively, a purified vitamin A alcohol in sesame oil, and a fourth lot of the concentrate dissolved in fish liver oil and subjected to heat inactivation of the vitamin A, as well as sesame oil, were all without antihypertensive effect. Likewise the second lot of the concentrate showed no prophylactic effect in experimental renal hypertension.

3. No toxic effects were observed in the dogs.

4. Obviously the antihypertensive effect of the first lot of the concentrate was not due to vitamin A but to some unknown constituent not present in the second and third lots.

5. Since this antihypertensive substance was effective by mouth and apparently in small amounts, further work leading to its reproduction and identification is highly desirable.

14227

Supra-Diaphragmatic Section of the Vagus Nerves in Treatment of Duodenal Ulcer.*

LESTER R. DRAGSTEDT AND FREDERICK M. OWENS, JR.

From the Department of Surgery, University of Chicago.

Much of the experimental work on the pathogenesis of gastroduodenal ulcer that has appeared in recent years is in harmony with the concept that the cause of these ulcers is the corrosive action of the gastric juice. It has been adequately demonstrated that pure gastric juice can destroy and digest living tissues including the wall of the stomach itself, producing in this case a defect which appears to be identical with the lesion encountered in man.[1] Under normal conditions, the gastric wall is not digested away apparently because it is not exposed to pure gastric juice. Food, which in the normal individual is the stimulus for the formation of gastric juice, is also the chief factor which protects the tissues against

* This work has been aided by a grant from the Douglas Smith Foundation for Medical Research of the University of Chicago.

[1] Dragstedt, L. R., *Arch. Surg.*, 1942, **44**, 438.