vals between the regular feedings, the blood sugar remains much lower but the lactic acid reaches and maintains an abnormally high concentration.

In an individual with a normal liver both monosaccharides help to maintain the blood sugar at a normal level. In glycogen storage disease of the liver the two sugars behave differently. Absorbed levulose is quickly removed from the portal blood by the liver and stored there as glycogen or fat, but cannot be released later as glucose to sustain the falling blood sugar. Glucose, on the other hand, is removed with difficulty from the portal blood by the liver;[7] therefore, during the absorption of glucose the blood sugar rises to a high concentration and then falls rather rapidly, due to the removal of glucose from the blood by tissues other than the liver for combustion or storage. The only way to raise the low blood sugar in the postabsorptive state is to feed more glucose. This explains the hypoglycemia when the extra sugar fed is levulose and the normal or high blood sugar when the extra sugar is glucose. It does not explain the high blood lactic acid after the blood sugar has been low for some time, nor the much lower blood lactic acid after the blood sugar has been normal for a few hours.

Under the conditions of the test the lactic acid content of the blood is only slightly more than normal as long as the blood sugar is within the normal range, but increases several fold when the blood sugar is maintained at an abnormally low level. Neither patient shows any of the recognized causes of anoxia, nor any of the symptoms that characterize this condition, nor does either patient show any symptoms of hyperadrenalinemia.

The inference would appear to be that prolonged hypoglycemia causes the breakdown of liver glycogen in the cases reported as it does in the livers of normal individuals. However, in von Gierke's disease the liver is unable to dephosphorylate hexosemonophosphate and discharge glucose into the blood. Blocked at this point the breakdown takes the alternate route, namely, levulose-6-phosphate to levulosediphosphate, etc.[8] In this case one of the end products would be lactic acid.

[7] Mason, H. H., and Andersen, D. H., *Am. J. Dis. Child.*, 1941, **61**, 795.

[8] Cori, C. F., *Biol. Symposia*, 1941, **5**, 131.

14225

Effect of *p*-Aminobenzoate and Methyl *m*-Amino-*p*-hydroxybenzoate on Acute Toxicity of *m*-Amino-*p*-hydroxyphenylarsenoxide in Mice.

LAWRENCE PETERS. (Introduced by A. D. Welch.)
From the Department of Pharmacology, Medical Research Division, Sharp and Dohme, Inc., Glenolden, Pa.

p-Aminobenzoic acid (PAB) has been shown by Sandground[1] to antagonize the single-dose fatal toxicity of a number of pentavalent organic arsenicals in rats. That this antagonism was probably not due alone to phenomena dependent on close structural similarity was indicated by the fact that acetarsone (sodium *m*-acetylamino-*p*-hydroxyphenylarsonate) was one of the arsenicals antagonized. More recently, and coincidental with the completion of the work reported here, Sandground[2] reported success in antagonizing the toxicity of "at least one of the trivalent arsenical antisyphilis drugs" with PAB; the identity of the compound was not disclosed, however.

The toxic signs observed by Sandground, and which were attributable to the pentavalent arsonic acids antagonized by PAB, were of the neurotropic type characteristic of this class of compounds. Since it is clear that some

[1] Sandground, J. H., *Science*, 1943, **97**, 73.

[2] Sandground, J. H., PROC. SOC. EXP. BIOL. AND MED., 1943, **52**, 188.

reduction to the analogous arsenoxide derivatives takes place *in vivo*,[3] the ability of PAB to antagonize the toxicity of the widely used antisyphilitic arsenical compound, *m*-amino-*p*-hydroxyphenylarsenoxide ("Mapharsen," Parke, Davis Co.), has been studied. Also, the ability of *m*-amino-*p*-hydroxybenzoic acid, as its methyl ester ("Orthoform," Winthrop Chemical Co.), to perform a similar role has been investigated.

Procedure. Martin and Thompson[4] found the antagonistic effect of cysteine and ascorbic acid to the acutely toxic effects of arsphenamine in mice to be most pronounced when the antagonists were administered several hours before the arsenical. A similar procedure was employed in these experiments in order to allow adequate time for the diffusion of PAB and methyl *m*-amino-*p*-hydroxybenzoate, Orthoform, throughout the tissues.

White mice of both sexes were used, PAB and Orthoform were given in doses which were experimentally demonstrated to be definitely sublethal. PAB was given as a solution of the sodium salt (pH 6.8 to 7.2) and Orthoform a suspension in 0.1% mucilage of tragacanth. Controls given a tragacanth suspension without drug showed no ill effects and the toxicity of Orthoform in this vehicle and in olive oil was the same. Tragacanth was chosen for convenience of administration. The Mapharsen was injected as an aqueous solution into the tail vein.

Results. Deaths began to occur in mice within one to 2 hours following an intravenous injection of lethal doses of Mapharsen; the majority of deaths occurred during the first 24 hours. No deaths occurred after 72 hours although the mice were observed for 10 days. The results are shown in Table I.

The concentration of free PAB in the blood of a number of mice was determined by the sulfonamide method of Marshall and his coworkers,[5,6] using *p*-toluenesulfonic acid as the protein precipitant.

Discussion of Results. The small difference in mortality rates in Experiment 1 and 4 is not considered significant. Although larger and equal numbers of animals would be required fully to substantiate this opinion, no antagonism of significance could be represented by such a small decrease in mortality. Furthermore there was no difference in the time of death of mice receiving Mapharsen alone and in those receiving Mapharsen plus PAB. The data on the concentration of PAB

TABLE I.
Acute Toxicity of Mapharsen in Mice, with and without the Previous Administration of PAB or Orthoform.

Exp.	Mapharsen per kg	PAB per kg	Orthoform per kg	Interval between doses	Deaths in 24 hours No.	Deaths in 24 hours %	Total deaths No.	Total deaths %
1	35.0 mg	0 g	0 g		15/20	75	16/20	80
	"	1 i.p.	0	2 hr	12/19	63	13/19	68
	"	0	0.5 i.p.	2 "	10/16	62	12/16	75
2	"	0	0		13/17	76	14/17	82
	"	2 i.p.	0	1½ "	12/16	75	13/16	81
3	32.5 mg	0	0		13/30	43	16/30	53
	"	0	0.5 i.p.	1 "	20/28	71	25/28	89
4	35.0 mg	0	0		15/18	83	15/18	83
	"	1 oral	0	1½ "	11/15	73	11/15	73
5	"	0	0		11/15	73	11/15	73
	"	1 i.p.	0	1 min	12/15	80	12/15	80

[3] Murgatroyd, F., Russell, H., and Yorke, W., *Ann. Trop. Med. Parasit.*, 1934, **28**, 227.

[4] Martin, G. H., and Thompson, M. R., *Exp. Med. Surg.*, 1943, **1**, 38.

[5] Bratton, A. C., and Marshall, E. K., Jr., *J. Biol. Chem.*, 1939, **128**, 537.

[6] Marshall, E. K., Jr., Litchfield, J. T., and White, H. J., *J. Pharm. and Exp. Therap.*, 1940, **69**, 89.

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

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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.