of alloxan. In 3 animals possessing only the adrenal cortex hypoglycemic convulsions did not occur following the injection of alloxan; one of the 2 animals tested showed an initial hyperglycemia. That extra-adrenal chromaffine tissue was not responsible for this protection against the hypoglycemia of convulsive level is demonstrated by the fact that hypoglycemic convulsions occurred in 2 alloxanized animals from which adrenal cortices had been removed. It would seem that the hypophyseal-corticoadrenal mechanism antagonizing the action of insulin is concerned in the initial reaction to the injection of alloxan.

*Summary.* An initial hyperglycemia did not appear in either adrenalectomized or hypophysectomized rats injected with alloxan. With the doses of alloxan used, hypoglycemic convulsions did not appear in any of 15 intact animals whereas convulsions occurred within 6 hr in all of 14 adrenalectomized and 9 of 10 hypophysectomized animals. In the absence of the adrenal medulla the reaction to alloxan was the same as in intact animals; removal of the adrenal cortex (regenerated cortex following adrenal enucleation) resulted in the same reaction as total adrenalectomy.

14930

## Effect of Mapharsen on Bromsulphalein Retention in Normal Dogs.*

VICTOR A. DRILL AND TED A. LOOMIS. (Introduced by William T. Salter.)

*From the Department of Pharmacology, Yale University School of Medicine, New Haven, Conn.*

Various arsenicals have been used as experimental agents to produce and study hepatic damage. Thus, liver injury produced by arsphenamine has been studied in relation to the protein, carbohydrate and fat content of the diet.[1,2] More recently methionine has been reported to counteract the increased icterus index produced by Mapharsen in *protein depleted dogs*.[3] Recently we studied the effect of oxophenarsine hydrochloride (Mapharsen) on the liver function of *normal dogs* and noted (1) that the bromsulphalein retention produced by a single injection of Mapharsen varied considerably and (2) that the dogs rapidly acquired a tolerance to Mapharsen, as judged by the rapid return of the liver functions to normal on subsequent injections.

*Methods.* The dogs used in the experiments were healthy adult animals receiving a stock diet of Purina chow. After control bromsulphalein determinations were made on the animals each dog was injected intravenously with 0.06 g of Mapharsen in 10 cc of distilled water. Bromsulphalein determinations were then made 6 hr and 24 hr after the Mapharsen injection. In some of the dogs the Mapharsen injections were repeated at weekly intervals. The 5 mg/kg dose of bromsulphalein was used to estimate the degree of hepatic dysfunction, and the reported readings were read directly against the 2 mg standards. Therefore, by using the 2 mg standard the retention values may range above 100%. The control dye retentions were between 5 and 12%, so that any retention above 15% was considered as evidence of decreased liver function.[4]

*Results.* Of 17 dogs injected with 60 mg of Mapharsen, 59% showed a retention of bromsulphalein 6 hr later. A bromsulphalein test 24 hr after the mapharsen injection showed

* Aided by a grant from the Fluid Research Fund of Yale University School of Medicine. The authors also wish to thank Dr. Oliver Kamm of Parke, Davis and Company for the Mapharsen used in the experiments.

1 Schifrin, A., *Wirchows Arch. path. Anat.*, 1932, **287**, 175.

2 Messinger, W. J., and Hawkins, W. B., *Am. J. Med. Sc.*, 1940, **199**, 216.

3 Goodell, J. P. B., Hanson, P. D., and Hawkins, W. B., *J. Exp. Med.*, 1944, **79**, 625.

4 Drill, V. A., and Ivy, A. C., *J. Clin. Invest.*, 1944, **23**, 209.

TABLE I.
Effect of a Single Injection of 60 mg of Mapharsen on Bromsulphalein Retention in Normal Dogs.

| Dog | Weight kg | Mapharsen mg/kg | % Bromsulphalein Retention Control | After Mapharsen 6 hr | 24 hr |
|---|---|---|---|---|---|
| | | Normal hepatic function | | | |
| 1 | 22.2 | 2.7 | 12 | 8 | 10 |
| 2 | 18.6 | 3.2 | 10 | 12 | 10 |
| 3 | 13.1 | 4.6 | 10 | 10 | 5 |
| 4 | 10.5 | 5.7 | 8 | 12 | 8 |
| 5 | 9.8 | 6.1 | 8 | 8 | 8 |
| 6 | 9.1 | 6.6 | 5 | 8 | 10 |
| 7 | 9.1 | 6.6 | 5 | 10 | 8 |
| | | Hepatic damage | | | |
| 8 | 17.7 | 3.4 | 8 | 30 | 30 |
| 9 | 16.1 | 3.7 | 10 | 35 | 22 |
| 10 | 13.9 | 4.3 | 10 | 45 | 15 |
| 11 | 10.9 | 5.5 | 12 | 45 | 30 |
| 12 | 10.8 | 5.6 | 8 | 150 | 125 |
| 13 | 9.5 | 6.3 | 12 | 60 | 30 |
| 14 | 9.5 | 6.3 | 10 | 60 | 8 |
| 15 | 9.3 | 6.5 | 8 | 60 | 15 |
| 16 | 7.7 | 7.8 | 10 | 25 | 12 |
| 17 | 6.6 | 9.1 | 10 | 80 | 80 |

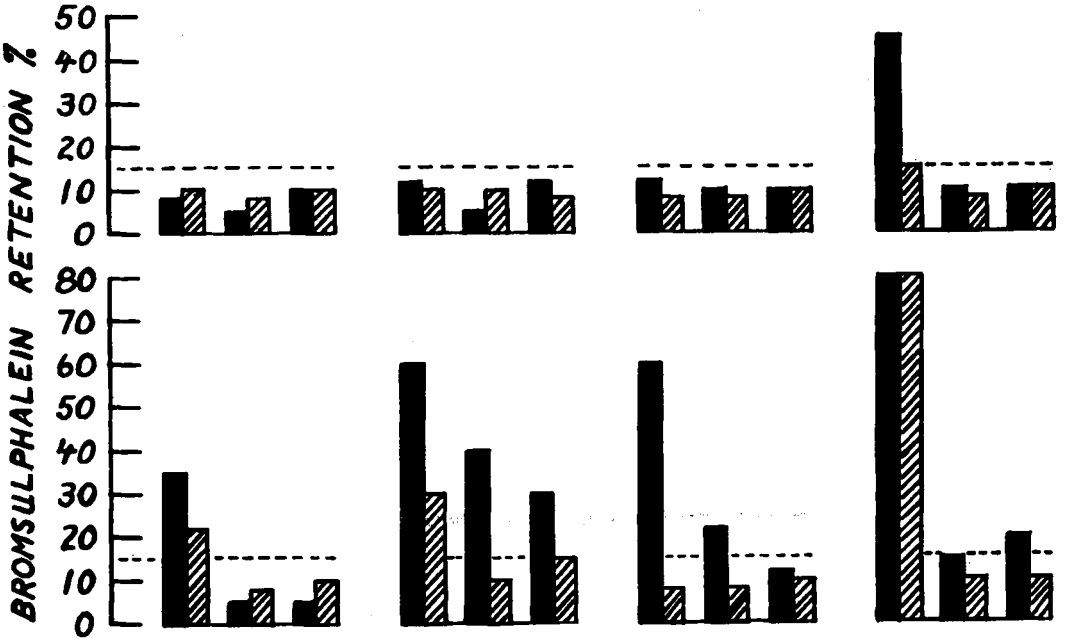


FIG. 1.
Effect of 3 injections of 60 mg of mapharsen given at weekly intervals on bromsulphalein retention of 8 dogs. Broken horizontal line indicates upper limit of normal of dye retention. Solid bar and hatched bar indicate dye retention tests 6 hours and 24 hours, respectively, after Mapharsen injection.

that the abnormal dye retention had decreased or had already returned to normal (Table I). When the dose of Mapharsen was calculated on a body weight basis no correlation between dosage and functional impairment was observed, over the range studied (Table I).

The effect of 60 mg of Mapharsen, given once a week for 3 weeks, was studied in 8 of the

above dogs (Fig. 1). Three of the dogs did not show an increased bromsulphalein retention after the first injection of Mapharsen and subsequent injections also failed to produce demonstrable change. The remaining 5 dogs showed an increased retention of bromsulphalein following the first injection of Mapharsen. However, after the 2 subsequent injections, tolerance had increased in these dogs so that the bromsulphalein retention either approached or returned completely to normal (Fig. 1).

*Discussion.* Normal dogs are said to tolerate 6 to 8 mg of Mapharsen per kilo without developing liver injury, as judged by the icterus index.[3] Using the bromsulphalein test impairment was detected with doses of Mapharsen as low as 3.4 mg/kg. Thus the bromsulphalein test may be more sensitive than the icterus index in detecting functional hepatic damage in dogs produced by Mapharsen. As can be seen from Table I there is also a marked variation in the liver function response following the injection of Mapharsen, so that in a smaller series of dogs one may easily obtain either a high or low percentage of the dogs showing hepatic damage. When Mapharsen was injected at weekly intervals, dye retention which occurred following the first injection was less following each additional injection. Therefore, one cannot test a given drug against Mapharsen toxicity by injecting Mapharsen one week, and Mapharsen with the substance to be tested the following week. Rats, rabbits and dogs have been reported to acquire a tolerance to certain organic arsenicals,[5] and the present study shows a similar tolerance with respect to the liver function of dogs.

*Summary.* Fifty-nine per cent of 17 normal dogs developed an abnormal liver function after a single injection of 60 mg of Mapharsen. The dye retention occurred irrespective of dosage over a range of 2.7 to 9.1 mg/kg of body weight. Dogs showing hepatic dysfunction from an initial injection of Mapharsen, subsequently showed less dye retention or a complete return to normal on 2 subsequent injections. Dogs having a normal bromsulphalein retention after one injection of Mapharsen also showed a normal dye retention following two subsequent injections.

[5] Kuhls, M. L., Longley, B. J., and Tatum, A. L., *J. Pharm. and Exp. Therap.*, 1939, **66**, 312.

## 14931 P

## The Prolonging Action of Penicillin by Para-Aminohippuric Acid.*

LEO LOEWE, PHILIP ROSENBLATT, ERNA ALTURE-WERBER, AND MARY KOZAK.
(Introduced by B. Kramer.)

*From the Department of Medicine and the Department of Laboratories, Jewish Hospital of Brooklyn.*

The successful treatment of certain infectious diseases with penicillin, notably those in which the offending organism is resistant to the drug, certainly is compromised by the wasteful manner in which the human body disposes of penicillin. Beyer, Flippin, Verwey, and Woodward[1] have proposed para-aminohippuric acid as an agent which aids the economy whereby penicillin is utilized by the body. They report that this substance competes with penicillin for the same tubular excretory mechanism and their simultaneous intravenous administration results in augmented blood penicillin levels. In view of the fundamental importance of this observation, it was considered worthy of clinical application in cases of subacute bacterial endocarditis particularly in those patients who were refractory to our standard dosages of penicillin.[2] Limited supplies of para-aminohippuric acid† did not permit extended studies to be made, however, and consequently only preliminary observations are being reported.

*Procedure.* The subjects received penicil-

* Aided by grants from friends of the Hospital and the Dazian Foundation for Medical Research.

1 Beyer, K. H., Flippin, H., Verwey, W. F., and Woodward, R., *J.A.M.A.*, 1944, **126**, 1007.