sion in the absence of dialysis was also reported by Muirhead, Grollman and Vanatta (9) (range +10 to +50 mmHg for 8 dogs, average +30 mmHg), Orbison, Christian and Peters(10) (average +37 mmHg for 7 dogs), and Muirhead, Stirman and Jones(1) (average +38 mmHg, for 8 dogs). These various results are comparable to those of the experiments herein reported.

Grollman *et al*(8) demonstrated no change in the cardiac index in canine renoprival hypertension of 8 to 59 days duration as derived in association with intermittent peritoneal lavage. The hypertension was interpreted as due to increased peripheral vascular resistance. The present experiments demonstrate that canine renoprival hypertension developing over 4 days time and in the absence of dialysis is also associated with elevated peripheral vascular resistance. Thus, acute renoprival hypertension of this type (in association with dietary protein and parenteral sodium) appears due to increased tone of resistance blood vessels (small arteries and arterioles), and as such, resembles the renal type of experimental hypertension.

Summary. Renoprival hypertension of the dog is definite within 4 days of bilateral nephrectomy when the animal is given dietary protein, parenteral sodium and does not exhibit excessive vomiting and diarrhea (weight loss minimal). Ten dogs with renoprival hypertension also exhibited an elevation of the peripheral vascular resistance. In acute canine renoprival hypertension, increased tone of resistance vessels appears to contribute in a major way to the hypertensive state. In this respect, the hypertension resembles experimental hypertension of renal type.

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Received May 14, 1965. P.S.E.B.M., 1965, v120.

Modification of Norepinephrine Tachyphylaxis by Guanethidine.* (30451)

GERHARD H. MUELHEIMS AND KENNETH E. WALTER†

Department of Medicine, St. Louis University School of Medicine, the Institute of Medical Education and Research, St. Louis City Hospital, St. Louis, Mo.

Tachyphylaxis to norepinephrine and epinephrine, as gauged by a decreasing pressor response, has been demonstrated by several investigators(1,2). Rosenthale and DiPalma (1) for example reported that, in order to maintain the blood pressure in dogs 30 to 40 mmHg above control levels during a three-hour infusion of norepinephrine the rate of the infusion of norepinephrine has to be increased at least 5 times and in many animals more than 20 times the initial dose. Recently it was reported from this laboratory that guanethidine elicits a marked pressor response after tachyphylaxis to norepinephrine has developed and not only restores but seems to enhance the pressor effect of ad-

* This study was supported by a grant from St. Louis Heart Assn. and USPHS General Research Support Grant of St. Louis University.

† Postdoctoral Fellow of Am. Heart Assn.

TABLE I. Difference in Average Pressor Response (mmHg) After Norepinephrine Injections 1-5 and 16-20 in Control and Guanethidinized Group of Dogs.

Control	Guanethidine
50.0	10.0
46.0	34.0
15.0	1.0
59.0	17.0
105.0	5.0
42.0	23.0
Avg: 53.0 ± 12.0*	Avg: 15.0 ± 5.0*

* S.E. of mean. t-test non-paired experiments: $p < 0.02$.

ministered norepinephrine(3). These findings suggested that it would be of interest to investigate the possibility that guanethidine‡ may prevent or delay tachyphylaxis to norepinephrine.

Methods. Twelve dogs weighing 5.5 to 10.5 kg were anesthetized with sodium pentobarbital (30 mg/kg i.v.). Six of the animals had received 15 mg/kg of body weight of guanethidine, intravenously, one day prior to the experiments. The other 6 served as controls. All dogs were vagotomized and ventilated with a Harvard respiration pump. The mean arterial blood presure was measured from the left femoral artery with a Statham transducer and continuously recorded by a Sanborn oscillograph. Norepinephrine, 0.05 mg of the base/kg of body weight, in 1 ml of 0.9% NaCl solution, was injected rapidly into the femoral vein at intervals of 5 minutes. Twenty such injections into each dog were made and the difference between the average pressor response to the initial 5 norepinephrine injections and the average pressor response to the last 5 norepinephrine injections was determined in the control dogs and in the dogs that previously had received guanethidine.

Results and discussion. As can be seen from Table I the mean difference between the average pressor responses of the initial and final 5 norepinephrine injections was 53 ± 12§ mmHg in the control group of animals, whereas, it was 15 ± 5§ mmHg in the group of dogs previously injected with guanethidine. In other words, the pressor response to norepinephrine decreased markedly in the control group of animals whereas it remained essentially unaltered in the guanethidinized dogs. This would seem to indicate that guanethidine maintains the pressor response to norepinephrine, *i.e.*, delays tachyphylaxis to norepinephrine. It should be mentioned that throughout the series of norepinephrine injections the pre-injection blood pressure levels fell in both groups of animals. The average mean blood pressure of the animals treated with guanethidine decreased from 121 ± 4§ mmHg to 72 ± 12§ mmHg, whereas, in the control group the blood pressure decreased from 125 ± 9§ mmHg to 94 ± 21§ mmHg.

One may wonder about the possibility that the effect of a pressor agent might vary with the pre-injection blood pressure level and that for example the higher the control blood pressure the smaller the response of a pressor agent may be or vice versa. The fact that the pre-injection blood pressure levels were not extreme and not greatly different from one another seems to exclude this possibility as the cause for the difference in the pressor response to norepinephrine of the two groups. It would therefore appear that the greater average pressor response to the final 5 injections of norepinephrine in the treated animals was due to guanethidine itself.

The mechanism by which guanethidine maintains the pressor response to norepinephrine is not entirely clear, particularly since an adequate explanation of the mechanism of tachyphylaxis to norepinephrine has not yet been offered. Rosenthale and DiPalma(1) have reported that the hemoconcentration, the decrease in blood volume and cardiac output as well as the acidosis occurring during a norepinephrine infusion are not the cause of norepinephrine tachyphylaxis. Similar experiments designed to demonstrate a role of the autonomic or central nervous system have been unsuccessful(1). Recently Burn and Rand(4) advanced the hypothesis that the decreased sensitivity to norepinephrine may be due to the fact that during an infusion of norepinephrine, the drug is taken up by "some kind of store in the blood vessel

‡ Kindly supplied by Ciba Pharmaceuticals, Inc.

§ S. E. of mean.

wall," from which it is slowly released and blocks the receptors through which the effect of norepinephrine is thought to be mediated. Indeed it has been found that catecholamines can be stored in tissues innervated by sympathetic nerve fibers and that these tissues can take up a considerably greater amount than their usual catecholamine content(5). Furthermore, it has been reported that the loss of norepinephrine from tissues which occurs after sympathetic denervation results in supersensitivity to the amine(6).

A similar increase in sensitivity to norepinephrine occurs after guanethidine(7) and this might possibly explain the delay in norepinephrine tachyphylaxis observed in the present study. The mechanism of this type of hypersensitivity, however, does not seem to be explained by the properties of guanethidine, which are concerned with depletion of tissue catecholamines and interruption of sympathetic transmission(8,9). Indeed, while both guanethidine and reserpine deplete tissues of catecholamines the acute sensitization to norepinephrine is observed only after guanethidine(8,10). Furthermore, the pressor response to norepinephrine is increased after guanethidine in reserpinized dogs and in dogs with spinal cord section(11). These facts would seem to favor the hypothesis that a direct action of guanethidine on the receptors might account for the potentiating effect of the catecholamine.

On the other hand, Hertting *et al*(12) have demonstrated in acute experiments that in guanethidinized animals administration of H^3-labeled norepinephrine results in an elevation of norepinephrine plasma levels and a decrease in tissue concentration of norepinephrine. Therefore, by exposing the receptors to a higher plasma level of norepinephrine guanethidine might effect a greater pressor response of norepinephrine.

Summary. Pressor responses to repeated injections of norepinephrine were recorded in a control group of dogs and in dogs pretreated with guanethidine. The results indicate that guanethidine maintains the pressor response of norepinephrine, *i.e.*, delays tachyphylaxis to norepinephrine.

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Received May 14, 1965. P.S.E.B.M., 1965, v120.

Selenium and Rabbit Skeletal Muscle Aldolase and Myosin.* (30452)

KENNETH P. MCCONNELL AND D. M. ROTH

Radioisotope Service, Veterans Administration Hospital and Biochemistry Department, School of Medicine, University of Louisville, Louisville, Ky.

There is a relationship between nutritional selenium deficiency and muscular dystrophy, since a selenium deficient ration will produce muscle dystrophy in lambs(1,2) and cattle (3,4). Muth(4), as well as others(5,6), has shown that sodium selenate when fed to sup-

* This investigation was supported in part by grant A-4445 from Nat. Inst. Health.