

Effect of Rigid Sodium Restriction on Blood Pressure and Survival of Hypertensive Rats.

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During the course of our studies on experimental hypertension in the rat, we have investigated the effects of various types of diets on the blood pressure. In view of the demonstrated effects of excessive amounts of certain amino-acids (particularly cystine) on the kidney, it was thought possible that these effects might be reflected by changes in the blood pressure. The effect of diets varying in their composition, or those in which the vitamin or amino-acid contents were altered, showed relatively little or no effects on the blood pressure. The addition of sodium chloride even in very excessive amounts to the normal diet also raised the blood pressure only slightly. On the other hand, when diets which were naturally low in sodium content were administered without the addition of the usual salt mixture, prompt reduction in the blood pressure occurred to relatively normal levels. The effect of the restriction of the sodium content of the diet on the blood pressure was so impressive as to warrant the experimental trial of such diets in the treatment of human hypertensive patients as described elsewhere.¹ The present paper is limited to our results on the experimental animal.

Methods. Our studies have utilized the rat for reasons discussed elsewhere.² Renal hypertension was induced by the procedure described previously.³ A stock diet (Rockland Farm rat ration) was powdered and di-

alyzed to remove the diffusible constituents. The food was powdered, suspended in water and placed in Visking tubing. The filled tubing was then placed in cylinders through which a stream of cold water circulated. After 4 or 5 days, tests for chloride in the suspension were negative. Because this procedure induced the loss of diffusible vitamins and inorganic salts other than sodium, the dried dialyzed diet was modified by the addition of synthetic vitamins (thiamin, riboflavin, hexabione, calcium pantothenate and niacin), cod-liver oil and the salt mixture of Osborne and Mendel⁴ from which all sodium salts were excluded.

Results. Fig. 1 shows a typical experiment in which a marked decline in blood pressure is induced in the hypertensive rat by the dialyzed diet described. Similar declines in blood pressure were observed following administration of the following substances, either singly or in mixtures: soy bean meal, peanut flour, cooked potatoes, rice, starch and gelatin. All of these substances are naturally low in sodium content.

Fig. 2 shows a decline in blood pressure brought about in groups of 6 rats fed on diets composed entirely of ground peanuts, soy beans, and potatoes. When sodium chloride in sufficient amount was added to these diets or to the dialyzed stock diet, the declines in blood pressure did not occur. The effect of sodium chloride is also shown in Fig. 3, in which the responses to diets of rice with the addition of varying amounts of sodium chloride are indicated. It appears that even 0.5% sodium chloride partially prevents the hypotensive effect of a low-sodium diet, and that 2% sodium chloride completely inhibits the effect. When potassium chloride was

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¹ Grollman, A., Harrison, T. R., Mason, M. F., Baxter, J., Crampton, J., and Reichsman, F., *J. Am. Med. Assn.*, in press.

² Grollman, A., *New York Acad. Sci.*, 1945, in press.

³ Grollman, A., *PROC. SOC. EXP. BIOL. AND MED.*, 1944, **57**, 102.

⁴ Osborne, T. B., and Mendel, L. B., *J. Biol. Chem.*, 1919, **37**, 557.

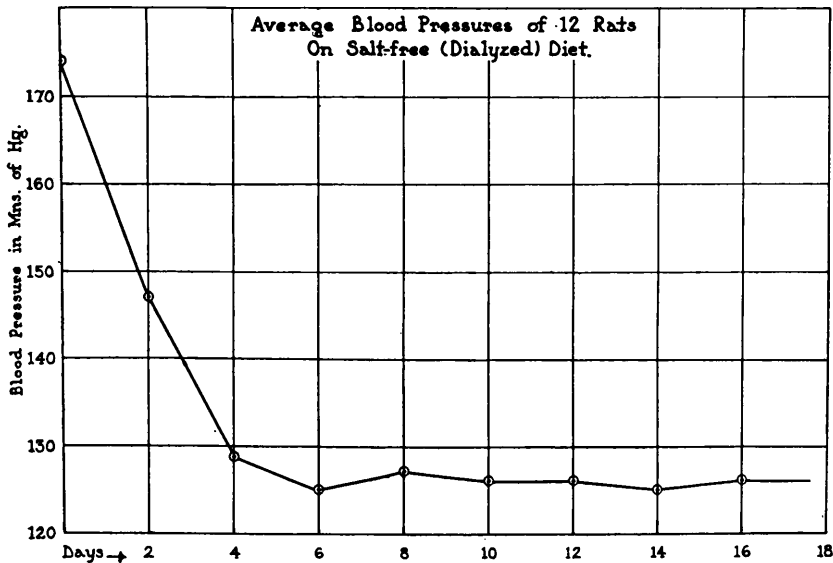


FIG. 1.

The effect of a diet practically free of sodium on the blood pressure of a group of 12 hypertensive rats. The ordinates are averages of the mean pressures on all 12 animals; the abscissæ, days during which the animals were maintained on the diet.

Effect of Certain Limited Diets on the Blood Pressure of Rats.

(Each curve equals average blood pressure of 6 rats)

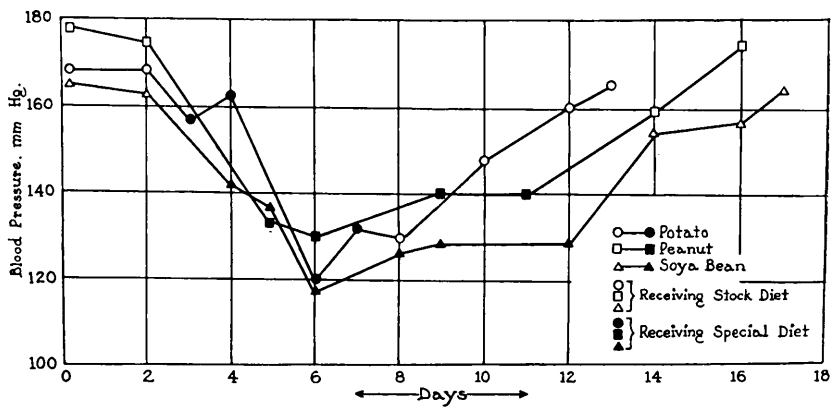


FIG. 2.

The decline in blood pressure which resulted from diets limited to potato, peanut, and soy bean is shown. When the stock diet was resumed the blood pressure rapidly rose toward the pretreatment level.

added to these diets in place of sodium chloride the blood pressures still declined. Hence, as shown in Fig. 4, it appears that deficiency of sodium rather than of chloride is related to the observed hypotensive effect. It should be emphasized that these significant declines in blood pressure were observed in hypertensive animals but not in animals with normal blood pressures in which sodium restric-

tion over short periods of time induces no perceptible drop in blood pressure. Conversely the addition of excessive amounts of sodium chloride to normal diets also as previously shown⁵ fails to increase the blood pressure of hypertensive or normal rats.

⁵ Grollman, A., Harrison, T. R., and Williams, J. R., Jr., *J. Pharm. and Exp. Therap.*, 1940, **67**, 76.

SODIUM RESTRICTION IN HYPERTENSION

The Hypotensive Effects of a Rice Diet as Modified by the Addition of Varying Amounts of Sodium Chloride
(Each curve equals the average blood pressure of 6 rats.)

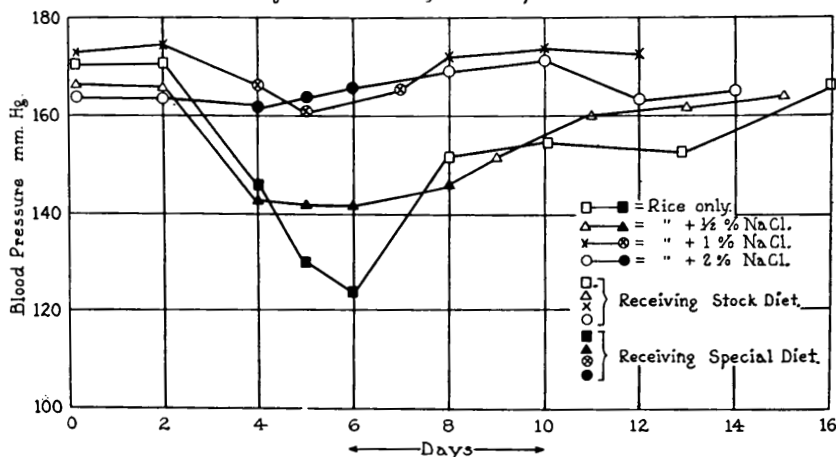


FIG. 3.

When the diet consisted of rice only a well marked decline in blood pressure occurred. The addition of sodium chloride in increasing amounts caused progressive inhibition of the decline in blood pressure.

Comparison of NaCl and KCl
When added to Soya Bean Diet

(Each curve equals average blood pressure of 6 rats)

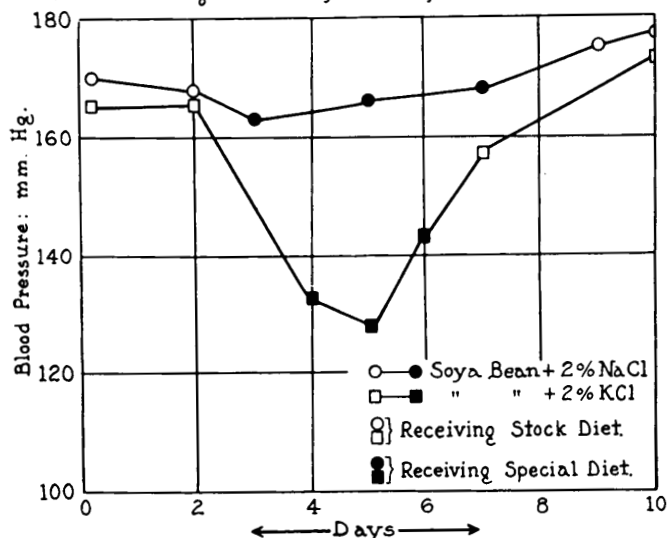


FIG. 4.

The addition of sodium chloride inhibited the hypotensive effect of the soya bean diet. Potassium chloride had no such effect.

Effect on Survival. In order to determine whether or not the marked reduction in blood pressure induced by sodium restriction for long periods is deleterious to previously hyper-

tensive animals, 62 hypertensive rats were divided into two equal groups, matched as to their blood pressures. One group received dialyzed stock diet, supplemented with salts

and vitamins, as described above, and the other received the regular stock diet. At the end of the 100-day period during which this experiment was continued, 15 of the treated animals survived as compared to only 8 of the control group.

The experiment just described seems to indicate that the decline in blood pressure associated with a low-sodium diet is not only not detrimental to animals with experimentally induced hypertension but appears to be beneficial insofar as duration of life is concerned.

Inhibitory Effect of Choline. Among the various vitamins which we have tested for their effect on the blood pressure, choline appeared to exert a slight but definite pressor action in animals with a mild degree of hypertension. When the substance was administered in high dosages (3% of the dried weight of the diet) together with a low sodium diet, the usual drop in blood pressure was not elicited. The mechanism of this inhibitory effect is not clear but unless one assumes that choline in large doses interferes with the excretion of sodium by the kidney of the hypertensive animal, we must consider the effect as possibly being due to the pharmacodynamic action of choline in such large doses.

Discussion. Many studies are available⁶ on the effect of the restriction of salt on the

blood pressure of human hypertensives but no previous study of this subject has been made on the experimental animal. Although the results on the human have been equivocal,⁷ the present study can leave little doubt as to the possibility of reducing the blood pressure of the hypertensive rat by rigid sodium restriction. The mechanism whereby this effect is induced is not established. It is known that there is an accumulation of salt and water in the tissues of the hypertensive patient, which was designated by Ambard⁸ as a "dry edema." It would appear most likely, therefore, that when subjected to a drastic sodium restriction the animal with experimental renal hypertension and certain (but by no means all) patients with hypertension rid themselves of the plethora of salt and water in their tissues and that this secondarily results in the observed reduction in blood pressure.

Summary. Drastic sodium restriction was shown to result in a marked drop in the blood pressure of rats with experimental hypertension. This drop in blood pressure was demonstrated to be accompanied by a prolongation of the survival of the animals. The drop was inhibited by the administration of large doses of choline.

⁷ Fishberg, A., *Hypertension and Nephritis*, Lea and Febiger, Philadelphia.

⁸ Ambard, L., and Beaujard, E., *La Semaine Med.*, 1905, **25**, 133.

⁶ Allen, F. M., and Sherrill, J. W., *J. Metab. Res.*, 1922, **2**, 429.

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Penicillin Resistant Staphylococci.

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Cultures of staphylococci may readily be made resistant to penicillin *in vitro* as demonstrated by various workers.^{1,2} Rammelkamp

and Maxon¹ and others^{3,4} have also shown that staphylococci may acquire a fastness to penicillin in the human body during the course of therapy with this agent. Further work is necessary before one can safely at-

¹ Rammelkamp, C. H., and Maxon, T., *Proc. Soc. Exp. Biol. and Med.*, 1942, **51**, 386.

² McKee, C. M., and Houck, C. L., *Proc. Soc. Exp. Biol. and Med.*, 1943, **53**, 33.

³ Gallardo, E., *War Medicine*, 1945, **7**, 100.

⁴ Lyons, C., *J. Am. Med. Assn.*, 1943, **123**, 1007.