allels the observation of Cheng and Sayers(1) in non-diabetic rats. These authors suggest that the mechanism of this change is most likely through inhibition of the pituitary output of diabetogenic factors, although direct competition with 11-oxy-steroids must also be considered. The estimation of the changes in output of 11-oxy-steroids by diabetics receiving DOCA will throw additional light on this problem. Further observations on the dynamics of this reaction in humans are in progress.

Summary. The effect of DOCA on the insulin sensitivity of 6 insulin insensitive patients was studied. Five showed a marked increase, and one an equivocal increase in insulin sensitivity.

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Production of Hypertension in the Rat by Substituting Hypertonic Sodium Chloride Solutions for Drinking Water.* (17583)

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A disturbance in the metabolism and distribution of salt and water in animals made hypertensive by the Goldblatt technique and its modifications and in essential hypertension may be inferred from a considerable body of recent work. An increase in the volume of extracellular fluid has been demonstrated in the muscles of hypertensive dogs;(1) polyuria and polydipsia are noted in renally hypertensive rats;(2) increased excretion of antidiuretic hormone has been reported in hypertensive dogs, rats and men;(3) the movements of extracellular fluids in rats made hypertensive by subtotal nephrectomy in response to the administration of hypertonic solutions are altered from the normal.(4) In free choice experiments hypertensive rats voluntarily reduce their sodium chloride intakes,(5) and rigid sodium chloride restriction lowers the blood pressures of hypertensive rats.(6) The utilization of low sodium diets in the therapy of hypertensive disease in man has been reviewed recently,(7) and the hypertensive patient reacts to the withdrawal of dietary sodium chloride in a manner different from the normal.(8) It appears possible, from a consideration of the known effects of adrenal steroids on the extracellular fluid, that the hypertension resulting from the administration of desoxycorticosterone acetate and sodium chloride(9) may also be associated with a disturbance in the extracellular fluids. Although it was originally believed that this type of hypertension might be explained by the renal lesion resulting from the procedure,(10) this view has become untenable in the light of recent evidence which indicates that such

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hypertension may persist in the absence of the kidneys(11) and that it is promptly reversible on the removal of DOCA implants.(12) Furthermore, the rapid disappearance of hypertension in animals with Goldblatt hypertension subjected to bilateral adrenalectomy,(13, 14,15) a phenomenon for which adequate explanation is still lacking, may be associated with the effects of adrenalectomy on the extracellular fluid.

The possibility that there may be an etiological relationship between a disturbance in the extracellular fluid and hypertension has recently been emphasized by Covian and Braun-Menendez(16) who found that after bilateral nephrectomy certain rats developed hypertension, and that the appearance of this hypertension appears to be related to an increase in the volume of the extracellular fluid whether this occurs spontaneously or is produced by the administration of sodium chloride solutions. The possibility that disturbance of the extracellular fluid may be of etiological significance in hypertension has been the subject of investigations in this laboratory. In the present report experiments are described which were designed to test the hypothesis that the extracellular fluid disturbance might be duplicated and hypertension induced by presenting animals with solutions of sodium chloride, in *concentrations sufficient to tax the regulatory functions of the kidney,* as a substitute for the drinking water. Although it has not proved possible to induce or to aggravate hypertension in the rat or in man by the administration of large quantities of sodium chloride,(17,18,19) the important factors of controlled water intake and sufficient prolongation of the experiment have not been achieved in any experiments on mammals. Lenel, Rodbard and Katz(20) have produced hypertension in the chicken by the substitution of isotonic and slightly hypertonic solutions for the drinking water, but similar results have not been reported for the mammal.

Experimental. Rats of the USC strain were used in these experiments. In 3 experiments adult males, young females and adult females were used. The animals of Experiments I and III weighed 200-250 g at the start of the experiment, those of Experiment II weighed 100 to 125 g. After a preliminary period in which body weights, fluid intakes and blood pressures were determined, the animals were divided into control and experimental groups. Blood pressures were determined with the aid of the Sobin tail plethysmograph.(21) The experimental animals received sodium chloride solutions from graduated drinking bottles as their sole source of fluid while control animals received tap water. In Experiment I sodium chloride concentrations of 1.5 to 2.5% were given; in Experiment III 2.0% sodium chloride solutions were used throughout; in Experiment II, which was conducted in the hottest part of the summer, the animals received 2.0% sodium chloride through most of the experimental period, but refusal of the salt solutions and precipitous weight losses on very hot days necessitated the substitution of tap water for 24 hour periods on several occasions. For the most part, salt concentrations of 2.0% were well tolerated by the animals; edema was never observed and diarrhea occurred only occasionally.

Blood pressures, body weights, and fluid intakes were followed for 6 weeks after the institution of the hypertonic sodium chloride regime. At the end of this period the animals

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TABLE I.
Systolic Blood Pressures and Organ Weights of Rats Receiving Hypertonic Sodium Chloride Solutions as Substitute for Drinking Water.

Exp. No.	Treatment	No., sex of rats surviving 4-6 wk	Body wt terminal (g)	Fluid intake,* cc/rat/day	Systolic blood pressure* (mm Hg)	Heart wt × 1000 / Body wt	Kidney wt × 1000 / Body wt
I	Control	7 M	250	23	103 ± 2	3.04 ± .22	7.1 ± .52
	1.5-2.5% NaCl	12 M	216	61	136 ± 20	3.43 ± .31	9.0 ± .85
II	Control	10 F	179	50	101 ± 4	3.07 ± .22	8.4 ± .69
	2% NaCl (see text)	10 F	141	196	122 ± 13	3.99 ± .32	9.8 ± .95
III	Control	10 F	237	44	99 ± 6	3.09 ± .27	7.6 ± .28
	2% NaCl	9 F	165	111	138 ± 7	4.16 ± .45	11.4 ± 1.51

* All values represent means in the last two weeks of the experiment.

were sacrificed and the weights of hearts and kidneys determined. The results of the experiments are presented in the Table. Blood pressure measurements obtained in the early part of the experiment indicated that the rise of blood pressure occurred rather suddenly in any rat after a latent period of one to 4 weeks. Once hypertension appeared in any animal it persisted so long as the animal continued on the regime of hypertonic saline. Although the pressure readings in any animal showed considerable variability when hypertension was established, normotensive readings were obtained only infrequently after the initial appearance of hypertension. No definite trend toward aggravation of the hypertension could be discerned in examination of the protocols of individual animals in the period of the experiment although the average of the systolic pressures of the "salt" groups showed a tendency toward persistent rise as increasing numbers of animals became hypertensive.

At autopsy the experimental animals showed no gross abnormalities beyond the enlargement of the heart and kidneys relative to the body weight noted in the Table. Although it will be noted that the absolute weights of these organs do not show significant increases, we feel that we are justified in considering that a true cardiac hypertrophy has developed in view of the constancy of the relationship between heart weight and body weight in rats subjected to inanition.(*22*)

Discussion. From our results it is clear that arterial hypertension can be produced in the rat by the substitution of hypertonic saline solutions for the drinking water. It is our belief that the present results, taken in conjunction with some earlier findings in which one of us (LAS) was unable to produce hypertension by the continued administration of large quantities of isotonic salt solutions, and the work of others (see above) who have failed to produce hypertension by the administration of salt without controlling water intake, indicate that the ***ratio of sodium chloride to water intake rather than the amount of sodium chloride taken is the determining factor*** in the

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development of this type of hypertension. Further study is required to elucidate the mechanism of this hypertension. One possibility which suggests itself is that the hypertension is due to the synergism between large quantities of salt and the endogenous secretions of the adrenal cortex. We are inclined to doubt this view, for work now in progress indicates that "salt" hypertension is not abolished by bilateral adrenalectomy, in contradistinction to hypertension of the Goldblatt type. Another possible interpretation is that the development of renal hypertrophy may result in a relative renal ischemia with the evocation of hypertension of the Goldblatt type. We consider this view unlikely, for we have noted no significant lesions in the kidneys of our hypertensive animals beyond the hypertrophy.

Although, as noted above, there is considerable evidence that arterial hypertension of several types is associated with a disturbance in extracellular fluid, an exact characterization of the changes in the extracellular fluid in hypertension has not been made, nor are we at present in a position to state the nature of the changes in the body fluids which occur in animals watered with hypertonic saline solutions. Further investigations in these directions will be required before it will be possible to attribute any etiological significance to body fluid alterations in hypertension.

Summary and Conclusions. (1) In 3 experiments, systolic blood pressure measurements were made on 27 control rats and on 31 animals watered with hypertonic sodium chloride solutions for a period of 6 weeks.

(2) The animals watered with hypertonic saline solutions developed an arterial hypertension after a latent period of one to 4 weeks. At autopsy this was found to be associated with an hypertrophy of the heart and kidneys relative to body weight.

(3) Some possible mechanisms for the development of this hypertension are discussed.

(4) The substitution of hypertonic sodium chloride solutions for the drinking water affords a simple, inexpensive, and dependable method for the production of arterial hypertension in the rat.

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Relation Between Pantothenic Acid and Response to Growth Hormone in the Adult Rat. (17584)

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The experiment reported here was originally designed to test the response of rats on high fat and high carbohydrate diets to anterior pituitary growth hormone. During the course of the experiment it was discovered that the diets were deficient in pantothenic acid. This circumstance, when coupled with the injection of growth hormone, produced results that seemed sufficiently interesting to report.

Methods. Adult female rats of the Sprague-Dawley strain were used in this study. There were 7 rats in each group. One group was placed on a high fat, and the other group on a high carbohydrate diet. Each high fat animal was pair fed with a high carbohydrate animal of similar body weight. Differences in caloric value of equivalent amounts of the fat and carbohydrate sources were taken into account in the paired feeding in order to insure isocaloric intake between the animals of each pair. Both diets contained 20% protein as casein, inorganic salts, Wesson oil, cod liver oil, tocopherols, and B vitamins in excess. The high fat diet contained 37% Crisco and the high carbohydrate diet 74% sucrose. The rats were allowed a preliminary

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