and para-bromo derivatives of diphenhydramine has been appraised clinically. The collective data indicate that their antihistaminic activity is comparable to that of diphenhydramine. The incidence of drowsiness and atropine-like effects is low with the para-methyl derivative(6,7); it is insignificant with the para-bromo compound(8).

Summary. The antihistaminic, anticholinergic and musculotropic spasmolytic properties of the para-halogen, para-methoxy and some para-alkyl derivatives of 2-benzhydryloxydimethylethyl amine have been investigated. Para-substitution with methyl, ethyl and halogen atom results in an enhancement of antihistaminic activity, a decrease in acute toxicity, or both. It lowers the atropine-like action but does not produce a significant change in musculotropic spasmolytic activity.

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Hypoadrenalism: Steroidal Mediation of Sodium Action on Blood Pressure; Modification of Antiarthritic Response to Cortisone.* (18113)

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Considerable evidence has accumulated that both the sodium ion and the adrenal cortex are concerned to some extent with the maintenance of blood pressure levels in hypertensive patients(1-3). Although the rigid restriction of salt masks the pressor response of hypertensives to desoxycorticosterone(4), this type of observation does not establish the fact that alterations in sodium metabolism modify the arterial tension through an adrenal mechanism. It has been noted that the adrenals of rats on a reduced sodium intake may be smaller and different in color(5), temporarily depleted of ascorbic acid(6), and may show secretory changes(7) and (in nephritic animals) subcapsular hyperplasia (8). Furthermore, excessive salt, or liberal amounts in animals receiving desoxycorticosterone, has resulted in progressive structural and functional atrophy of the glomerular zone of the adrenal cortex(9,10). Finally, chromatographic patterns of urinary steroid excretion may be influenced by the salt intake(11).

In order to investigate further the possibility that sodium influences the blood pressure through steroidal action, studies were

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undertaken in a patient with uncomplicated hypertensive vascular disease and Addison's disease who also had mild diabetes mellitus and rheumatoid arthritis.

Case report and methods. G.S., a 55-year-old, white housewife, was admitted to the metabolism ward of the Presbyterian Hospital for research study. Hypertension was first recorded 10 years before admission, with repeatedly elevated blood pressure readings up to 210/110 mm of mercury. Addison's disease developed one year before entry, as demonstrated by weakness, skin and buccal mucous membrane pigmentation and the disappearance of hypertension. The diagnosis was clinically apparent and was substantiated by the finding of repeated serum sodium values which were markedly below normal limits following salt withdrawal, calcification in the adrenal areas by x-ray and abnormally low 17-ketosteroid (2.9 mg) and neutral reducing lipid values (0.9 mg)(12)† in 24-hour urine specimens. The administration of 50 mg of adrenocorticotropic hormone (Armour) failed to produce any lowering of the eosinophile count. Mild diabetes was first evident 7 years before, as manifested by hyperglycemia, glycosuria and decreased tolerance to glucose, but was adequately controlled by diet alone. The diagnosis of rheumatoid arthritis, although not substantiated serologically, was made on the basis of 10 years of characteristic distribution of joint pains and deformities, the typical pattern of stiffness after inactivity, and the absence of positive data favoring other types of arthritis. There was neither past nor present evidence of cardiac pain, congestive failure, renal or cerebral involvement. Funduscopic examination showed minimal arteriolar narrowing. Complete blood count and venous pressure were within normal limits. Popliteal arterial pressures were comparable to those obtained in the arms. X-ray of the heart disclosed no hypertrophy and the electrocardiogram showed no abnormalities. Repeated urinalyses were negative. The patient had no significant temperature elevation throughout the period of observation, and at no time showed signs or symptoms of congestive failure.

The methods employed were identical to those previously described(4,13), including the measurement of the "resting" blood pressure, except that the patient was allowed water *ad libitum* for the first 94 days always in excess of 2000 cc. Thereafter the fluid intake was kept constant at 4550 cc daily. She was provided with a constant diet containing 50 g of protein and 225 g of carbohydrate daily. A large salt intake was found obligatory to sustain normal serum sodium values. Although a constant sodium chloride intake could not be maintained exactly, interval chemical analyses showed that the intake ranged between 290 and 350 milliequivalents per day. Supplemental salt was provided in the form of enteric-coated tablets. Desoxycorticosterone acetate‡ (DCA) was administered subcutaneously in single daily doses, and cortisone§ intramuscularly in 3 divided doses per day.

Results. (Fig. 1) The patient was placed initially on a regimen of salt restriction (A). Hypoadrenalism was confirmed again by the appearance of nausea and increased weakness and a drop in serum sodium concentration to 128 milliequivalents per liter. Thereafter, by avoiding restriction of salt, serum sodium values were never permitted to fall below normal limits and she remained free of manifestations of adrenal cortical insufficiency.

The addition of 25 mg of cortisone daily (B) was accompanied by subjective improvement in the arthritis, definite objective increase in joint mobility and a progressive reduction in the erythrocyte sedimentation rate. After restoration of electrolyte equilibrium by the resumption of adequate salt, the administration of cortisone was associated with no other subjective changes, no further significant effects on salt and water balance, no gly-

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† We are indebted to Dr. Joseph W. Jailer for these determinations.

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‡ Supplied through the generosity of Dr. K. W. Thompson of Organon, Inc., Nutley, N. J.

§ Purchased from Merck and Co., from funds supplied by the U.S.P.H.S.

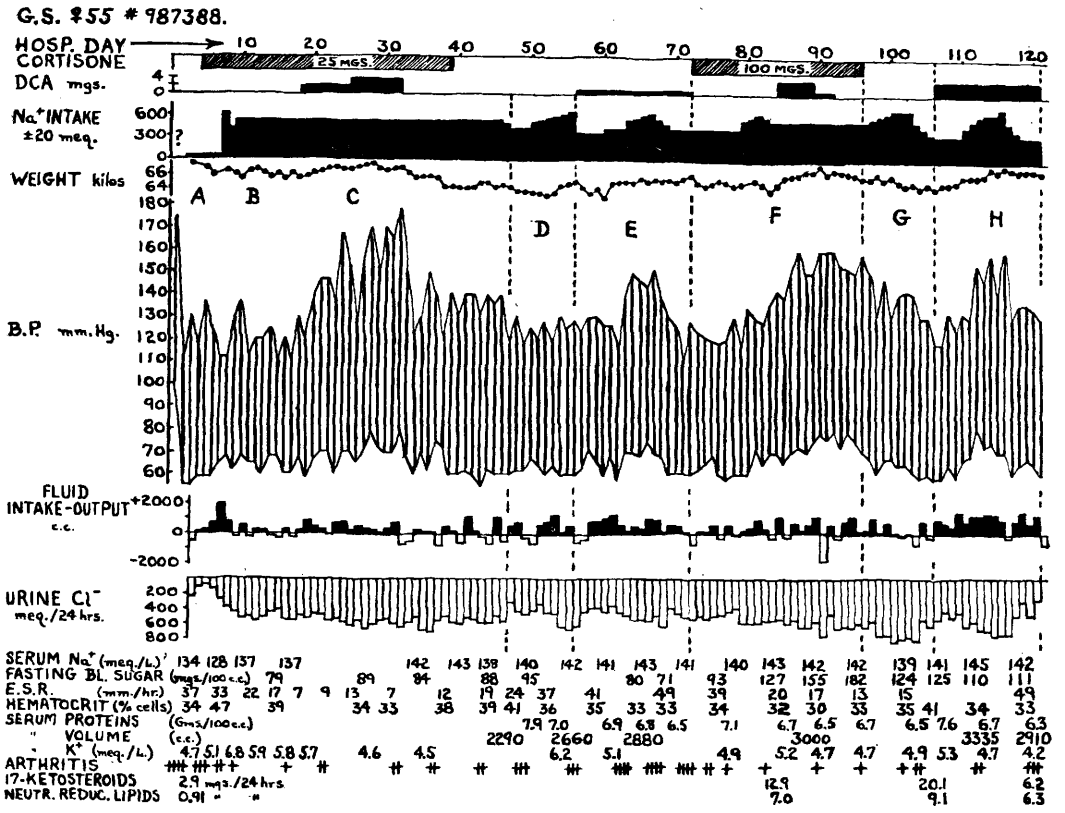

FIG. 1.
Summary of clinical and laboratory data.

cosuria and no change in fasting blood sugar levels. The "resting" blood pressure was unaffected. On the further addition of DCA (C), first 2 and then 4 mg daily, some hemodilution was observed and a rise in arterial tension was noted. The arthritis remained improved. Prompt diuresis and a rapid fall in blood pressure ensued after stopping the DCA but while the patient was still receiving cortisone. On discontinuing the latter steroid, the arthritis recurred slowly and the sedimentation rate increased.

A progressive increase in sodium chloride intake was instituted next (D). A peak ingestion of close to 40 g of salt was achieved without significant gastrointestinal symptoms. This was accompanied by some weight gain and hemodilution but no alteration in blood pressure. Simultaneously with reduction in the sodium chloride intake, the patient was placed on 1 mg of DCA daily (E). Again the salt dosage was increased, again hemodilution was evident, but this time with concomitant elevation of the arterial tension. On decreasing the sodium chloride intake, despite continuation of the steroid, the blood pressure fell promptly.

During the next 24 days (F) the patient received 100 mg of cortisone daily in divided doses with almost complete remission of her arthritic symptoms and a progressive decline in sedimentation rate. Slight rounding of the face, insomnia, weight gain, hemodilution and an increase in fasting blood sugar levels developed during this period. Presumably because of a high renal threshold, only inconstant minimal traces of reducing substances appeared in the urine. The 24-hour excretion of 17-ketosteroids rose to 12.9 mg, of neutral reducing lipids to 7.0 mg, after 11 days of cortisone administration alone. The blood pressure began to rise slightly before

the addition of DCA, apparently unrelated to changes in sodium chloride intake, continued its upward trend during 8 days of DCA therapy and did not show a significant fall until the cortisone was withdrawn.

Duplication of the type of study conducted in periods (D) and (E) was then undertaken. The blood pressure dropped progressively on discontinuing cortisone even though the sodium chloride dosage was increased to a peak of 42 g per day for a three-day period (G). With reduction in the sodium chloride intake, the patient was placed on 4 mg of DCA daily (H). Once more the "resting" blood pressure rose with increased salt dosage and fell promptly when it was decreased.

Casual blood pressure values were also recorded throughout the study. During all periods in which a pressor response was noted, casual readings reached definite hypertensive levels with diastolic values in the 90-110 range.

Discussion. The response of the arthritis deserves comment first. Although observations were limited to a single study, it is noteworthy that joint signs and symptoms were improved dramatically following a much smaller dose of cortisone than that generally effective in rheumatoid arthritis, and that 100 mg daily were of no greater value than 25 mg. This raises the possibility that the customary action of cortisone in rheumatoid arthritis is offset in part by other substances in the intact adrenal cortex or that its effect is augmented by the hypoadrenal state. There was no indication that the addition of DCA modified the response of the joint disease to cortisone in any respect, or, in the dosages employed, resulted in a paradoxical increase in sodium and chloride excretion(14).

The present study confirms the previously reported finding in a patient with hypertension and hypoadrenalism, in whom restoration of an elevated blood pressure could be achieved by DCA but not with salt alone(15). In addition, the rise in arterial tension, while the patient was maintained on 100 mg of cortisone, preceded the addition of DCA and persisted after the DCA was discontinued. This response supports the observation that cortisone may act as a pressor agent in the absence of the adrenals(13).

Finally, it was noted on 2 separate occasions that a high sodium chloride intake without steroid administration failed to modify the blood pressure. On the other hand, when maintained on either 1 or 4 mg of DCA daily, the blood pressure rose with an increased intake and fell when the salt dosage was reduced. The rise in blood pressure might be attributed to the greater hemodilution evident during the periods of DCA administration. Several arguments may be raised against such an explanation. The serum volume was only slightly greater in the first comparative period when receiving DCA. In the final period, the blood pressure fell abruptly to baseline levels on reducing the sodium chloride intake but the serum volume (2910 cc) remained at the levels achieved during the first trial with DCA and salt (2880 cc). Furthermore, we have noted repeatedly that over-treatment with salt and DCA in Addisonian patients may cause comparable degrees of hemodilution; however, hypertension in this group, if it is to appear, requires at least a week or two for its development and occurs long after maximal salt and water retention.

The failure of the blood pressure to rise with sodium chloride doses in excess of 40 g might reflect the presence of some unmeasurable vascular insufficiency or lack of responsiveness in the Addisonian patient. Yet this patient was in fluid and electrolyte equilibrium and salt in these amounts does not modify the blood pressure of normotensives.

The observation in this patient that the level of the blood pressure parallels the sodium chloride intake, providing a steroidal source is available, suggests that the action of sodium is mediated through an adrenal mechanism rather than through direct vasopressor action or by means of some independent renal pressor substance. Obviously, this relationship could be at any level of steroid metabolism, before or after degradation, or even through some change in excretion of final end-products

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by modification of renal function.

Summary. 1. Studies were undertaken in a patient with hypertensive vascular disease, Addison's disease, diabetes mellitus and rheumatoid arthritis. 2. The arthritis responded to smaller doses of cortisone than those generally effective. 3. Whereas large doses of sodium chloride failed to modify the blood pressure, the arterial tension rose and fell in conjunction with salt intake providing the patient was maintained on constant amounts of desoxycorticosterone acetate. 4. It is suggested that the action of sodium chloride on blood pressure is mediated through an adrenal mechanism.

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Use of Monosodium Glutamate for Improving the Palatability of Amino Acid Rations.* (18114)

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It has been observed repeatedly in this laboratory that mice and rats require several days to become accustomed to rations containing free amino acids as the source of nitrogen when fed *ad libitum*. During this adjustment period the animals consume less food and hence grow at a slower rate as compared with those which receive rations containing casein. In some instances a loss in weight occurs during the first 3 to 7 days. Maddy and Elvehjem(1) found that in spite of this lag in growth during the first week, mice that received a ration containing 16 amino acids exhibited growth rates during the second and third weeks that closely approximated those of animals which received a 19% casein ration. Ramasarma *et al.*(2) obtained similar results when rats were fed a ration containing 18 amino acids. Food consumption was variable and lower, and growth rates remained below those of the casein controls until the third week at which time considerable improvement was noted. The latter workers resorted to the force-feeding and paired-feeding techniques to insure equal nitrogen intakes. Over a period of 2 years we have obtained growth data on 200 mice representing 22 groups that have received *ad libitum* the amino acid ration of Maddy and Elvehjem. The final average weights of these groups ranged between 77 and 98% of those of the casein controls with most of the values being between 85 and 90%. The initial lag period was less pronounced in some groups than others, but it occurred without exception. These concordant findings indicate that a ration of amino acids is not as palatable to the mouse as is a casein ration. It appeared that growth during the first few days of the experimental period was critical in that animals which received the amino acid rations could not overcome completely the initial setback, and final weights rarely completely reached those of animals fed casein.

Since the techniques of force-feeding and paired-feeding are tedious when applied to large groups of animals or are objectionable for other reasons, attempts were made to improve the palatability of the amino acid ration. This report is concerned with the use of monosodium glutamate for this purpose.

Experimental. All mice used in these studies were males of the Webster Swiss strain and

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