DESOXYCORTICOSTERONE ACETATE

THE POTENTIATION OF ITS ACTIVITY BY SODIUM CHLORIDE*

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PLATES 5 TO 7

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Selye and his coworkers (1) have reported that the prolonged treatment of normal rats with massive doses of desoxycorticosterone acetate (DCA) and sodium chloride gives rise to the development of hypertension, nephrosclerosis, periarteritis, enlargement of the heart and kidneys, and other lesions. The degree of response, according to Selye, varies with a number of factors. Thus, an increase in the NaCl supplement of the diet, or preliminary excision of one kidney intensifies the changes described, as does the administration of anterior pituitary extract or thyroid extract. On the other hand, Selye has shown that the concurrent administration of NH_4Cl with NaCl and DCA tends to inhibit the development of vascular and renal damage. Masson and Beland (2) state that KCl did not have this effect.

Recent studies (3) concerning the effect of comparatively low dosages of certain adrenal steroids upon the course of cytotoxic serum nephritis in rats revealed that DCA (2.5 mg. daily) intensified the nephritic process. Furthermore, it was found that arterial hypertension developed in nephritic animals receiving DCA but did not appear in non-nephritic animals treated with the same dosage. In these studies, none of the animals developed arterial lesions similar to those described by Selye in normal rats receiving much larger amounts of DCA and NaCl. Nevertheless, all animals receiving DCA, both normal and nephritic, showed some degree of cardiac and renal enlargement and renal tubular changes, apparently similar to what was termed a "renotropic" effect by Selye and induced by him with methyl testosterone, thyroxin, and anterior pituitary extract. No "nephrosclerotic" changes of the type described by Selye were demonstrable with the dosage of DCA employed. Le Compte (14) has reported, following the administration of testosterone, enlargement of kidneys and intensification of anti-kidney serum nephritis, although no increase in blood pressure.

The present study was undertaken to determine primarily the influence of the withdrawal of the sodium ion from the diet upon the changes induced by

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DCA in normal rats and in rats with nephritis initiated with a rabbit anti-rat-kidney serum. It had been shown earlier (4) that the addition of KCl to the drinking water of normal animals treated with DCA prevented the usual decrease in serum potassium concentration and the intracellular replacement of potassium by sodium as well as a characteristic disturbance of striated muscle function (4, 5). Consequently, the effect of KCl upon the disturbances induced in normal and nephritic rats receiving relatively small amounts of DCA and NaCl was also observed.

TABLE I

Outline of Regimens Employed in Various Groups of Animals

Group	Diet	Drinking water		DCA daily	Anti-rat kidney serum
		NaCl	KCl		
		per cent	*per cent*	*mg.*	
I	Basic (low sodium)	0	0	2.5	0
II	Basic + 1.5 per cent NaCl	0.2	0	2.5	0
III	Basic + 1.5 per cent NaCl	0.2	0.2* 0.4	2.5	0
IV	Basic + 1.5 per cent NaCl	0.2	0	0	0
V	Basic	0	0	2.5	+
VI	Basic + 1.5 per cent NaCl	0.2	0	2.5	+
VII	Basic + 1.5 per cent NaCl	0.2	0.2* 0.4	2.5	+
VIII	Basic + 1.5 per cent NaCl	0.2	0	0	+

* KCl was given in 0.2 per cent dilution for first 3 weeks of study, then increased to 0.4 per cent for remainder.

EXPERIMENTAL

The animals used in this study were hooded rats of the Long-Evans strain, both males and females, ranging in age from 61 to 68 days.[1] They were maintained on the following diet: Whole wheat flour, 65.5 per cent; casein, 25 per cent; Wesson oil, 4 per cent; cod liver oil, 2 per cent; and calcium carbonate, 1.5 per cent. On analysis, this basic diet contained 0.89 m.eq. of Na per 100 gm., 1.91 m.eq. of Cl per 100 gm., and 6.17 m.eq. of K per 100 gm. In all groups, except those in which sodium restriction was desired, 1.5 per cent of NaCl was added to this basic diet.

The rats were divided into eight groups of eight, each composed of four males and four females. The treatment plan for each group is outlined in Table I.

The desoxycorticosterone acetate (DCA)[2] was suspended in peanut oil (10 mg. per cc.) and 2.5 mg. injected daily in different areas over the back.

The rabbit anti-rat-kidney serum employed to induce nephritis was prepared essentially as outlined by Smadel (6). In the present study, the serum was given intravenously on 2 con-

[1] One animal in the control group was only 32 days old at the start of experiment.

[2] DCA (DOCA) was furnished through the courtesy of Dr. Leo A. Pirk of Roche-Organon, Inc., Nutley, New Jersey.

secutive days, starting 6 days prior to beginning the injections of DCA, to animals in groups V, VI, VII, and VIII. The total dose employed was either 0.8 cc. or 0.9 cc., according to the weight of the animal. It had been established previously that this serum induced heavy albuminuria in rats of this strain when given in the doses employed.

Systolic blood pressure readings, using the plethysmographic method described by Williams, Harrison, and Grollman (7) were recorded on each rat for 1 to 2 weeks before starting the experiment, then at weekly intervals during the course of the study. The blood pressure was determined 10 times consecutively, and the average of these taken as the week's reading. The difficulties encountered in using this apparatus were several, and the most troublesome of these was the maintenance of a constant temperature. At too high a temperature, the rats became prostrated and an occasional young rat died during the preliminary period. On the other hand, at too low a temperature, either no reading was obtainable or one far below those previously recorded, as might be expected, since, with a plethysmographic method, full vascular dilatation is essential for comparable determinations. To obviate effects of temperature variation, readings were made in a constant temperature room set at 30°C., and to insure vasodilatation in the tail, an electric light bulb was placed within 1 foot of the apparatus. Unreasonably low readings were occasionally obtained in members of the various groups of animals and were probably due to inadvertent lowering of the room temperature. These readings have,nevertheless, been included in the compilation of Chart 1.

Qualitative or quantitative determinations of urinary albumin were made initially and again 3 weeks later in the first four groups, while in the groups receiving anti-kidney serum, they were made at the start of the period of observation and every 2 weeks thereafter.

At the completion of the study, which lasted 6½ weeks, the animals were weighed, anesthetized, and blood was withdrawn under oil, to be pooled with that of other rats in the same group for determination of sodium, potassium, total protein, and urea nitrogen. All determinations were made in duplicate. Butler and Tuthill's (8) method was used to obtain the sodium values. Potassium was determined by a modification of Shohl and Bennett's procedure described by Consolazio and Talbott (9). Total protein was arrived at using Moore and Van Slyke's (10) formula of relation of protein to specific gravity, and the latter figure obtained according to the gradient tube principle described by Lowry and Hastings. Urea nitrogen determinations were made by the micro-Kjeldahl technique.

Following blood withdrawal the animals were sacrificed and the heart, kidneys, and adrenals weighed. Portions of heart and kidney tissue were collected in weighed tubes according to group. The material was dried to constant weight to ascertain the water content and micro-Kjeldahl determinations were made on the dry tissue to obtain its nitrogen content (Table IV).

Slices of kidney tissue from groups V, VI, and VIII were frozen and studied for oxidative activity on glucose substrate by Dr. Eugene Knox. Other portions of heart, kidneys, adrenals, and liver were then fixed for histological study.

RESULTS

All animals gained weight and remained well during the course of the study, with two exceptions, both in groups VII (NaCl + DCA + KCl + serum): one animal suffered an injury to its jaw, leading to malocclusion, and as a result gained weight more slowly than its fellows; the second, at the end of 6 weeks, appeared moribund and when sacrificed was shown to have marked cerebral edema.

Blood Pressure.—The systolic blood pressure measurements are shown graphically in Chart 1. The solid middle line represents the average of the

weekly readings of all rats in each group, while the upper and lower broken lines designate weekly individual extremes. The development of striking hypertension was noted in all animals receiving NaCl (1.5 per cent NaCl in the diet and 0.2 per cent added to the drinking water) in addition to DCA and

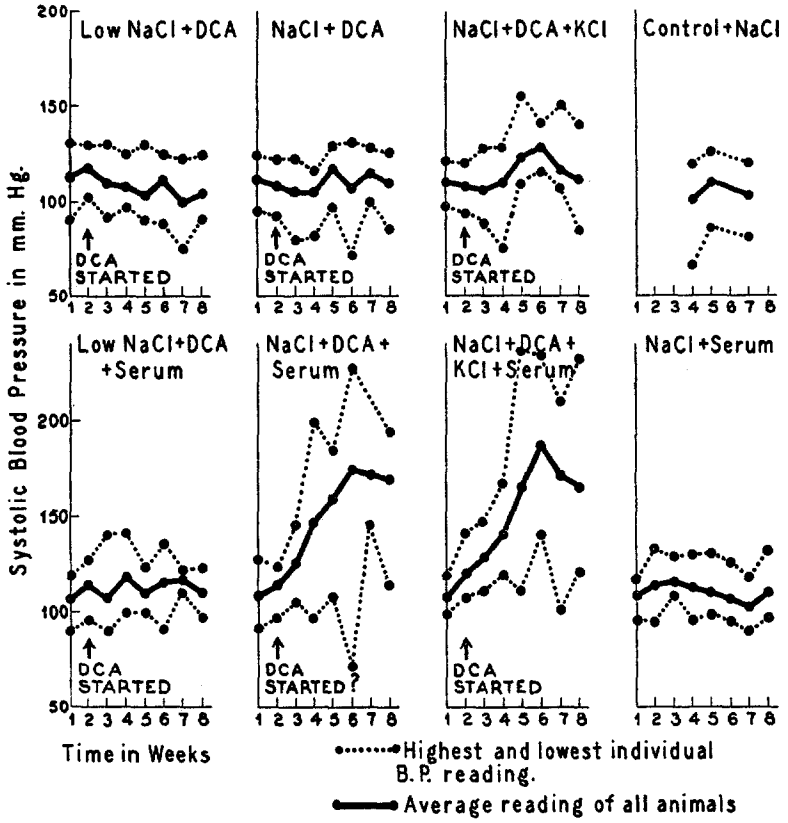

CHART 1. The effect of DCA, sodium chloride, and potassium chloride upon the blood pressure of normal rats and rats rendered nephritic with a rabbit anti-rat-kidney serum. Animal groups I, II, III, and IV are presented from left to right in the upper row of curves, and groups V, VI, VII, and VIII are presented in the lower row.

nephrotoxic serum, (*i.e.*, both group VI and group VII) with one exception. This was the undernourished animal with deformed jaw in group VII, which had a blood pressure reading as high as 140 on only one occasion. The addition of potassium chloride to the drinking water in either 0.2 per cent or even 0.4 per cent did not appear to modify significantly the development or the degree of hypertension. In the absence of any one of the three factors, *i.e.* a liberal sodium intake, DCA, or cytotoxic serum, no hypertension was observed consistently, although a single animal in group III (NaCl + DCA + KCl) had three readings of over 140 mm. Hg.

Albuminuria.—The urinary albumin determined qualitatively at the beginning of the study varied from 0 to +++, which is normal for this strain of rats. No alteration in the degree of albuminuria was observed in any animals in groups I, II, III, and IV; *i.e.*, rats not given nephrotoxic serum. Quantitative determinations of the urinary albumin done at random on approximately one-third of these rats averaged 1.3 gm. per liter. On the other hand, every animal receiving anti-kidney serum developed a definite increase in albuminuria and excreted an average of 10.6 gm. per liter at the end of the study. It was interesting to observe that in two-thirds of the animals the values obtained at the end of the first 2 weeks were significantly greater than the later ones. This apparent decrease in albuminuria was presumably due in part to dilution resulting from a great increase in water turnover in nephritic rats receiving NaCl and DCA or receiving both NaCl and KCl as well as DCA.

TABLE II

*Blood Chemistry on Pooled Sera**

Group	Diet and treatment	Serum Na	Serum K	Serum protein	Serum urea N
		m.eq./l.	*m.eq./l.*	*gm. per cent*	*mg. per cent*
I	Low NaCl + DCA	140.8	4.7	6.2	28
II	NaCl + DCA	145.7	2.9	6.2	14
III	NaCl + DCA + KCl	143.6	4.2	6.4	14
IV	NaCl − control	140.8	4.9	6.5	24
V	Low NaCl + DCA + serum	143.0	4.1	6.4	25
VI	NaCl + DCA + serum	147.0	3.3	6.3	23
VII	NaCl + DCA + KCl + serum	144.6	3.9	6.4	20
VIII	NaCl + serum	139.8	4.8	6.4	24

* Determinations made on pooled sera from 4 to 8 animals in each group.

Blood Analyses.—The values of sodium, potassium, total proteins, and urea nitrogen, as determined in each group from pooled sera, are shown in Table II.

Sodium.—It will be seen that the sodium figures in all eight groups varied within narrow limits. However, since the determinations were made on blood pooled from animals in each group, the variations from group to group may assume significance. It is evident that the highest sodium values were found in rats receiving both NaCl and DCA. The administration of potassium concurrently with NaCl and DCA was accompanied by less striking changes in sodium, while the restriction of NaCl (groups I and V) resulted in values which were essentially the same as the controls without DCA. No effect on serum sodium was noted which could be ascribed to the administration of anti-kidney serum alone.

Potassium.—Significant reduction in the serum potassium was observed in the rats treated with DCA and NaCl, whereas on the salt-poor regimen there was no comparable decrease despite the long continued administration of DCA.

The addition of KCl to the drinking water of animals receiving NaCl and DCA caused elevation of the potassium level, raising it almost to the normal values.

Serum Protein.—The total serum protein values in all eight groups were almost identical, indicating that there was no hemodilution attendant upon prolonged DCA administration such as had been reported in acute studies (16).

Nitrogen Retention.—There was no significant retention of urea nitrogen in any group.

Weights.—The average body and organ weights are shown in Table III. Values for males and females are recorded separately because of the marked differences in the size of the two sexes. It will be noted that the body weights

TABLE III

Body and Organ Weights

Group	Diet and treatment	Body weight		Heart		Kidneys		Adrenals*	
		gm. ♂	gm. ♀	mg. ♂	mg. ♀	mg. ♂	mg. ♀	mg. ♂	mg. ♀
I	Low NaCl + DCA	237	176	705	541	1603‡	1256	34	31
II	NaCl + DCA	258	183	894	671	2131	1568	27	34
III	NaCl + DCA + KCl	283	178	928	702§	2427	1646	31	39
IV	NaCl − control	238	174	685	595	1781‡	1222	36	47
V	Low NaCl + DCA + serum	243	174	772	598	1921‡	1400	25	34
VI	NaCl + DCA + serum	235	178	1120	815	2462	1835	27	36
VII	NaCl + DCA + KCl + serum	246	168	1059	790	2552	1912	33	33
VIII	NaCl + serum	261	174	816	578	2095	1473	35	44

Each value = average of four animals unless otherwise designated.

* Each value in the column = average of only two animals.

‡ Average of three animals; fourth animal, in each instance, showed the spontaneous hydronephrosis sometimes seen in males of this strain.

§ Average of three animals.

from group to group are comparable. As observed previously (1, 3) the hearts and kidneys of the animals receiving NaCl and DCA were strikingly heavier than those of the control group and in the hypertensive rats (given cytotoxic serum in addition to NaCl and DCA), these organs were, as noted before, even larger. There was a moderate increase in kidney size observed in animals treated with nephrotoxic serum alone, as has been reported elsewhere (3), but only questionable increase in heart weight. The addition of KCl did not counteract the tendency to cardiac and renal enlargement produced by NaCl and DCA, in fact, kidney weights were slightly greater in these groups than in those receiving NaCl and DCA alone. On the other hand, following the restriction of NaCl, no enlargement of the kidneys or hearts was found despite the long continued administration of DCA. Furthermore, the kidneys of

nephritic rats receiving DCA but no NaCl were possibly smaller than those of nephritic animals receiving a liberal complement of NaCl but no DCA.

Most of the male animals receiving DCA showed some decrease in the weight of the adrenal glands. The significance of these observations is doubtful since the adrenal glands of only two animals in each group were weighed.

Tissue Analysis.—In an earlier study (3) the question was raised as to whether the observed increase in weight of heart and kidneys attendant upon treatment with DCA and NaCl represented hypertrophy or edema. Table IV presents the results of determinations of water and tissue nitrogen content in each group. From this it is apparent that there is no edema of the cardiac tissue; *i.e.*, the water and nitrogen content of the tissues were the same in all

TABLE IV

*Tissue Analyses**

Group	Diet and treatment	Heart		Kidney	
		Water	Tissue nitrogen	Water	Tissue nitrogen
		per cent	*gm./kg. wet tissue*	*per cent*	*gm./kg. wet tissue*
I	Low NaCl + DCA	76.7	31.4	74.4	32.0
II	NaCl + DCA	76.7	32.0	74.8	31.4
III	NaCl + DCA + KCl	76.6	31.7	74.7	31.3
IV	NaCl − control	76.9	31.6	74.6	32.2
V	Low NaCl + DCA + serum	76.5	31.7	74.9	31.5
VI	NaCl + DCA + serum	76.9	30.9	77.0	29.3
VII	NaCl + DCA + KCl + serum‡	76.3	32.4	77.1	28.8
VIII	NaCl + serum	76.7	31.2	74.3	32.1

* Each value determined from pooled tissues of eight animals.

‡ Values in this group determined from pooled tissues of seven animals.

groups regardless of treatment. In groups VI and VII, the slight increase in water content and the corresponding diminution in nitrogen content suggest very slight water retention in the kidney tissue. This, however, is minimal and cannot account for more than a small fraction of the increase in organ weight. Consequently it is obvious that the enlargement of heart and kidneys following prolonged treatment with DCA and NaCl represents true hypertrophy.

Metabolic Activity of Kidney Tissue.—Studies of oxidative activity of kidney slices from groups V, VI, and VII were made by Dr. W. Eugene Knox. The Q_{O_2} on glucose substrate (O_2 uptake per mg. dry tissue per hour) was found to be equal in all three groups, confirming the view that kidney enlargement represented hypertrophy and not edema.

Histopathology.—Sections prepared from both kidneys of each animal

were examined. In general, the changes were comparable to those reported in previous studies (3). The cytotoxic serum nephritis (Fig. 2) and the lesions produced by DCA (Fig. 1) were classified from 1 to 4 plus according to the extent and the intensity of the alterations. The presence of any demonstrable focus of interstitial inflammation was classified as 1 plus cytotoxic serum nephritis. Kidneys exhibiting more extensive interstitial lesions associated with tubular and glomerular changes were graded from 2 to 4 plus. Similarly, the tubular lesions in DCA-injected animals were classified according to the degree of tubular distention and the intensity of the changes involving the tubular epithelium. These changes also have previously been described in

TABLE V

Type and Degree of Severity of Renal Lesions

Group	Diet and treatment	No. animals in group	Nephritic lesions*						DCA tubular lesions*	
			No. animals showing lesions	No. animals showing lesions of varying intensity					No. animals showing lesions	Range of severity of lesions
				0	+	++	+++	++++		
I	Low NaCl + DCA	8	0	8					3	0–++
II	NaCl + DCA	8	0	8					5	0–++++
III	NaCl + DCA + KCl	8	0	8					5	0–++++
IV	NaCl – control	8	0	8					0	—
V	Low NaCl + DCA + serum	8	3	5	2	1	—	—	2	0–+++
VI	NaCl + DCA + serum	8	8	0	2	3	2	1	4	0–++++
VII	NaCl + DCA + KCl + serum	8	7	1	0	2	4	1	6	0–+++
VIII	NaCl + serum – control	8	6	2	6	—	—	—	0	—

* For description of nephritic lesions and DCA tubular lesions, see accompanying text and figures.

detail (3). The results of the histologic examination are summarized in Table V. It is seen there that in groups I and V, the omission of Na from the diet reduced to a minimum the incidence and the extent of the typical changes that are observed following prolonged treatment with DCA. The addition of KCl to the drinking water had no such effect (groups III and VII).

As in previous experiments (3), a marked intensification of the nephritic lesions was found following the administration of DCA to animals receiving NaCl and injected with nephrotoxic serum (group VI). This enhancing effect of DCA was not influenced by the addition of KCl to the diet (group VII), but was inhibited when NaCl was omitted from the diet.

It is of interest that the effect of DCA on the adrenal cortex, as described by Selye (11) and by Carnes *et al.* (12) could also be correlated with the presence

or absence of sodium salts in the diet; *i.e.* in animals with salt restriction no atrophic changes in the subcapsular zone of the adrenal cortex were noted despite long continued administration of DCA (Figs. 3 and 4).

No periarteritic lesions of the type described by Selye (1) who employed larger doses of NaCl and DCA in normal or unilaterally nephrectomized rats could be found.

COMMENT

From the foregoing observations, it is apparent that DCA in doses of 2.5 mg. given daily for 6 weeks with NaCl, is capable of producing a series of striking anatomical and physiological disturbances in rats. In normal animals, the anatomical changes observed include hypertrophy of the heart and kidneys (without arterial hypertension), characteristic changes in the epithelium of the renal tubules, and atrophic changes in the subcapsular layer of the adrenal cortex (1, 3, 12). In animals rendered nephritic by means of a rabbit anti-rat-kidney serum, not only are the same changes observed, but in addition, the intensity of the nephritic process is greatly enhanced by DCA and the animals develop significant hypertension. The degree of hypertension appears to be correlated with the severity of the nephritic lesions. Furthermore, normal as well as nephritic rats receiving DCA and salt tend to have an elevation of the serum sodium concentration and exhibit a definite decrease in serum potassium concentration, but give no evidence of hemodilution, changes shown earlier to appear in dogs (13) as well as rats (5) receiving DCA over protracted periods of time.

The addition of KCl to the drinking water fails to prevent any of the gross or microscopic anatomical disturbances in DCA-treated rats, confirming the observation of Masson and Beland, nor does it prevent the development of hypertension in nephritic animals. It does, however, in the dosage employed, restore toward normal the depression of potassium in the blood serum.

The usual effects of long continued administration of DCA, in the dosage employed, are either completely abolished or sharply reduced in intensity if the animals are maintained on a diet which is virtually sodium-free. For example, the hearts and kidneys of animals receiving DCA but no salt are not larger than those of control animals receiving no DCA; there is no atrophy of the subcortical zone of the adrenal cortex and the changes in the renal tubular epithelium are minimal. Furthermore, the intensity of nephritis in animals receiving DCA but no NaCl is no greater than in animals not being treated with DCA, and hypertension does not develop in the absence of NaCl. Finally, a low salt diet prevents the fall in serum potassium and rise in sodium usually associated with prolonged treatment with DCA.

The mechanism by which NaCl potentiates the action of DCA is not apparent. It is tempting to assume that the toxic effects of DCA are in reality

the result of sodium "poisoning" or potassium depletion since this steroid is known to enhance the retention of sodium and cause excessive excretion of potassium by the kidneys. As stated above, it is well established that, with NaCl in the diet, protracted treatment of animals with DCA causes the serum electrolyte changes observed in the present study, and in addition it causes the partial replacement of intracellular potassium by sodium. The latter change is most marked in striated muscle (4, 5) and occurs to a lesser extent in cardiac muscle (5, 17). Replacement of potassium by sodium has not been observed in the smooth muscle of the stomach or uterus (17). It has been mentioned that the addition of 0.2 per cent KCl to the drinking water of dogs receiving DCA and salt restores the serum potassium concentration to normal and prevents the intracellular electrolyte disturbances described. In the present study the addition of KCl up to 0.4 per cent to the drinking water restored the serum potassium to levels only slightly below normal and yet it had no ameliorating effect upon the other striking disturbances resulting from the concurrent administration of DCA and NaCl. Consequently, it seems improbable that potassium depletion is responsible for the changes observed. Since the deviation of serum sodium levels from normal is not great in any of the groups of animals, particularly in those receiving KCl, it seems unlikely that this change alone can have great significance. Whether or not the changes following the long continued administration may be secondary to accumulation of sodium in the renal parenchyma has not been determined.

All animals receiving DCA and NaCl with or without KCl had a larger daily water exchange than did either rats receiving DCA with a low sodium intake or rats given NaCl but not treated with DCA. It would therefore seem possible that the changes observed might be referable to an increase in physiological demands upon the heart and kidneys. On the other hand, this seems unlikely since in diabetes insipidus, in which there is often a greater increase in water turnover than that observed in the present studies and usually an elevation of serum sodium concentration, lesions of the type observed in the present study have not been reported. Indeed, Swann (15) found that the kidneys and hearts of rats with diabetes insipidus drinking saline after posterior hypophysectomy were not enlarged. Whatever may be the mechanism responsible for the various changes induced by DCA, it is obvious that they are dependent upon a liberal supply of the sodium ion in the diet.

SUMMARY

1. Desoxycorticosterone acetate (DCA) and NaCl, in the dosage employed in normal rats, caused renal and cardiac hypertrophy, characteristic changes in the renal tubular epithelium, atrophic changes in the subcapsular zone of the

adrenal cortex, and serum electrolyte changes characterized by a rise in sodium and fall in potassium.

2. In rats rendered nephritic with a rabbit anti-rat-kidney serum, the same regimen caused similar changes. In addition, DCA given concurrently with NaCl greatly intensified the nephritic process and gave rise to striking arterial hypertension.

3. A diet, virtually sodium-free, administered to normal and nephritic rats receiving daily injections of DCA abolished or reduced to a minimum the effects of this steroid; *i.e.*, a liberal ingestion of NaCl was essential for the potentiation of the action of DCA.

4. The addition of KCl to the drinking water of rats receiving DCA and NaCl tended to correct the depression of the level of potassium in the serum, but had no effect upon the hypertension in nephritic animals nor upon the anatomical lesions.

5. The mechanism by which the sodium ion potentiates the activity of DCA has not been established.

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EXPLANATION OF PLATES

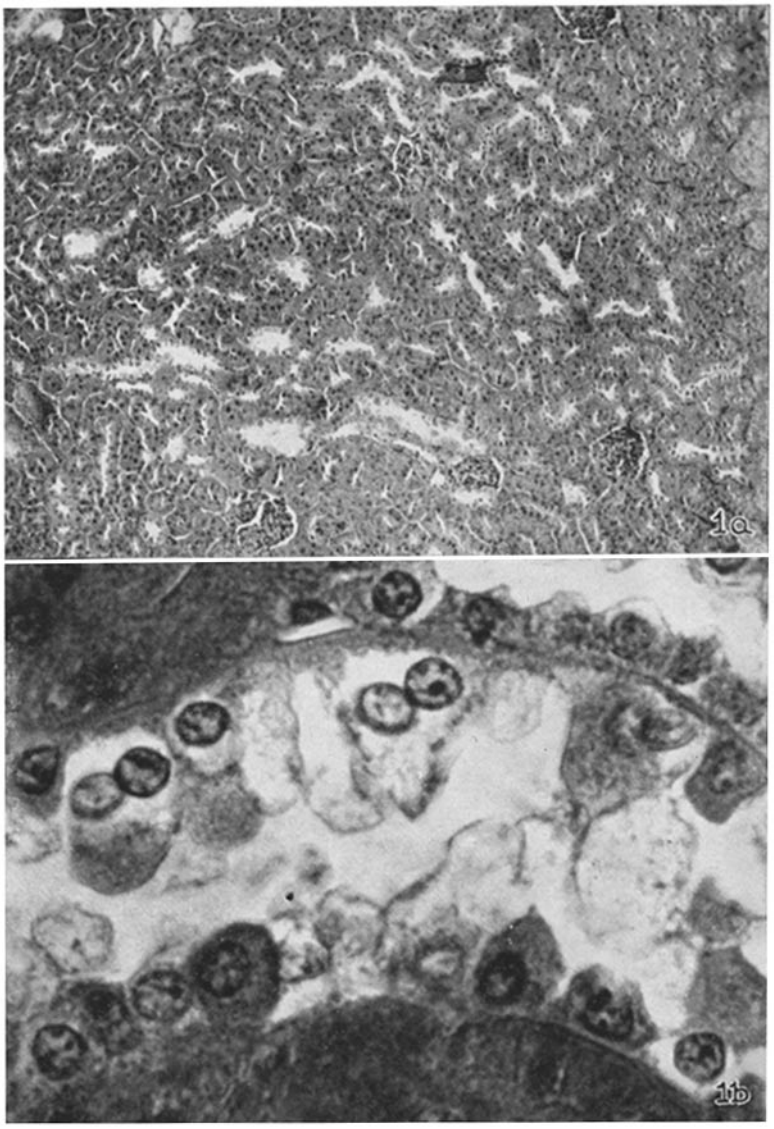
The sections were stained with hematoxylin and eosin.

PLATE 5

Kidney of an animal in group II receiving DCA + NaCl. Changes of this intensity were graded as 4 plus.

FIG. 1 *a*. Low power view showing distension of convoluted tubules. × 100.

FIG. 1 *b*. Swelling of tubular lining cells with vacuolization of cytoplasm. × 700.



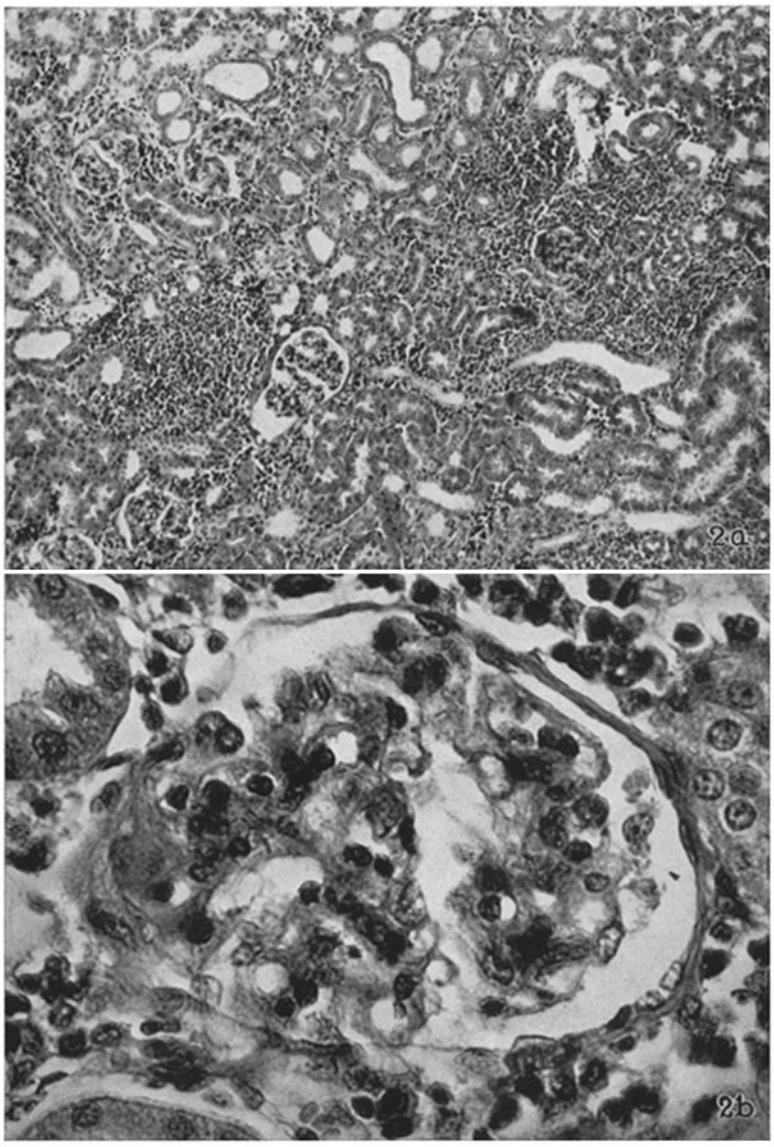
(Knowlton *et al.*: Desoxycorticosterone acetate)

PLATE 6

Kidney of rat of group VI, receiving cytotoxic serum + DCA + NaCl, representative of nephritic changes graded 4 plus.

FIG. 2 *a*. Low power view showing intense chronic interstitial inflammation. × 100.

FIG. 2 *b*. High power view of glomerulus with thickened basement membrane and adhesions between portions of tuft and glomerular capsule. × 300.

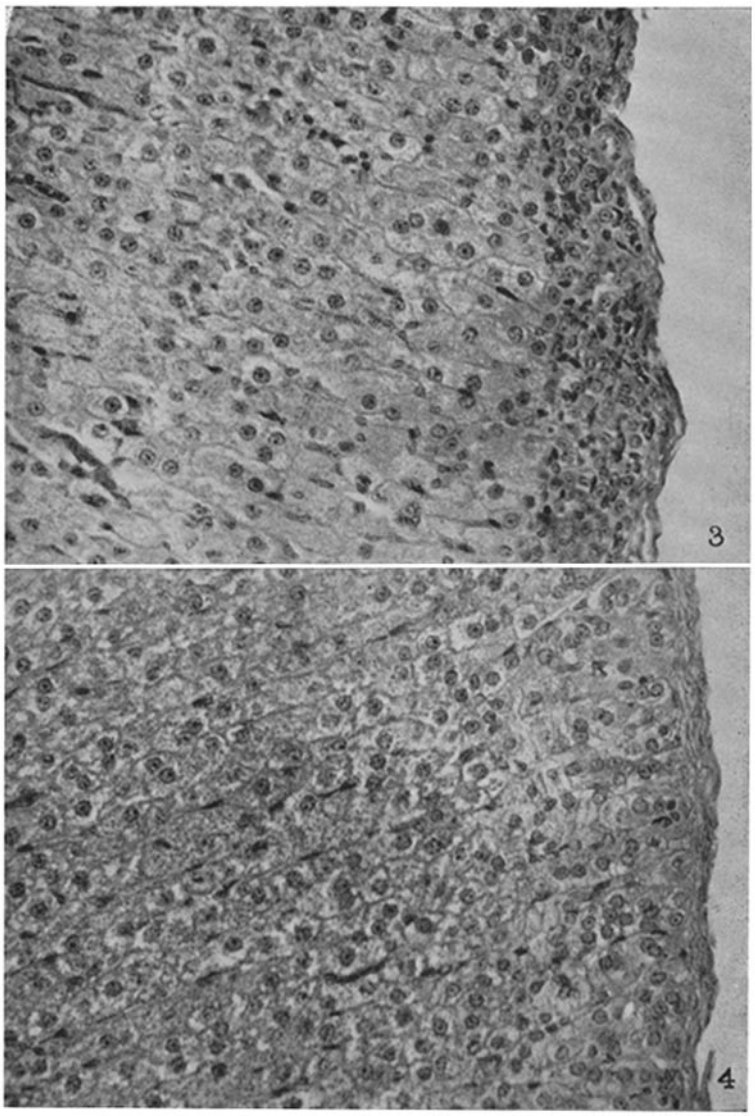


(Knowlton *et al.*: Desoxycorticosterone acetate)

PLATE 7

FIG. 3. Adrenal cortex of rat injected with DCA, maintained on a liberal intake of NaCl (group II). The subcapsular zone presents atrophic changes resulting in a sharp, characteristic demarcation from the subjacent cortical tissue. The cells of the subcapsular zone are reduced in size and display basophilia of cytoplasm associated with loss of foamy cytoplasmic structure. × 240.

FIG. 4. Adrenal cortex of rat in group I injected with DCA but maintained on a low Na ration. The subcapsular zone shows none of the changes seen in Fig. 3. The glandular tissue is indistinguishable from that of normal controls. × 240.



(Knowlton *et al.*: Desoxycorticosterone acetate)