The Development of Hypertension and Nephritis in Normal and Adrenalectomized Rats Treated With Cortisone.* (17556)

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The following studies were undertaken to determine the influence of cortisone upon the development of hypertension and nephritis in rats. Observations have been made upon adrenalectomized as well as intact animals.

Procedure. Twenty-three 2 to 3 months old male and female rats of the Long-Evans strain were divided into 3 groups. In the 8 animals in each of the first 2 groups the adrenals were intact, while the seven animals of the third group were bilaterally adrenalectomized at the beginning of the experimental period. The animals were fed a modification of the McCollum stock diet,(1) adjusted to contain 1.7% sodium chloride. In addition, all 3 groups received 0.85% saline as drinking water. All animals were injected intravenously on 3 successive days with rabbit anti-rat kidney serum,(2) totalling 0.8 cc. Group I received only the cytotoxic serum; Group II received, in addition, daily subcutaneous injections of 2.5 mg of cortisone starting one week prior to the administration of anti-kidney serum. In Group III, cortisone was begun 8 days after adrenalectomy and immediately following the anti-kidney serum injections, in the dosage of 5 mg daily; after the first week, the daily dose was reduced to 2.5 mg. Blood pressure determinations were made at approximately weekly intervals on all rats. The indirect plethysmographic method originally described by Williams, Harrison and Grollman(3) and later modified by Sobin(4) was employed and the results are recorded as previously outlined by these authors.(5) The growth of the animals was recorded. At the conclusion of the period of observation, 4 to 5 weeks after the administration of anti-kidney serum, the rats were anesthetized with ether, without prior fasting, then bled and sacrificed. Determinations of serum sodium were made using a flame photometer with an internal standard having an accuracy of ±1%.(6) In addition, determinations of urea nitrogen were made in all groups, and, in the 2 groups of intact rats, of serum carbon dioxide content, chlorides, sugar and total cholesterol using standard methods. The weights of heart, kidneys, thymus and the adrenal glands were recorded. No adrenal tissue was found in the operated animals (Group III). Sections of kidney were fixed in Zenker's fluid and stained with hematoxylin and eosin for histological study. Sections of the pituitary were stained by Masson's technic.

Results. In Fig. 1 growth curves are presented. In the adrenalectomized group a most

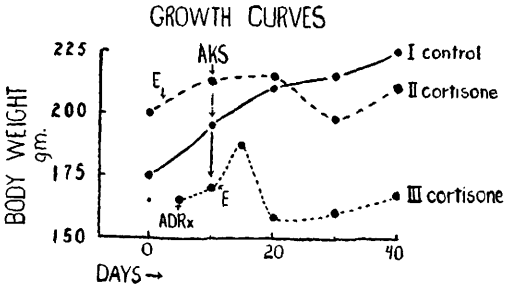

FIG. 1.

AKS = Rabbit anti-rat kidney serum.
ADR_x = Bilateral adrenalectomy.
E = Date on which cortisone injections were commenced.

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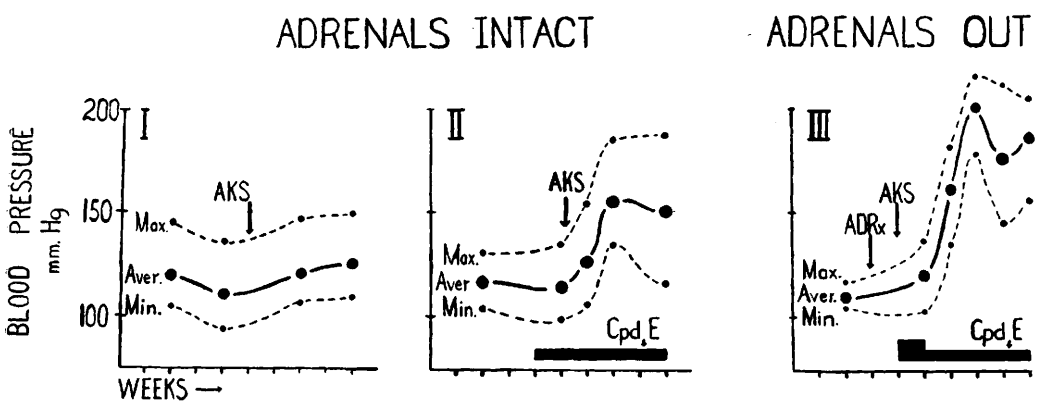

FIG. 2.

Effect of cortisone on the blood pressure of intact and adrenalectomized rats given anti-kidney serum.

Aver. = Avg weekly blood pressure of all rats in group.
Max. and Min. = Highest and lowest individual blood pressure readings each week.
AKS = Rabbit anti-rat kidney serum given at time indicated by arrow.
ADR_x = Bilateral adrenalectomy performed at time indicated by arrow.
Cpd E = Cortisone. Duration of administration indicated by solid black bar.

impressive weight gain was evident within the irst week after serum administration while the rats were receiving 5 mg of cortisone daily. This correlated with the development of edema in these animals. Subsequently and concomitantly with a decrease in cortisone dosage to 2.5 mg daily, the edema disappeared with a corresponding loss of weight. The differences in growth of Groups I and II are of doubtful significance, owing to the fact that the rats of Group II had attained greater growth than those of Group I when the experiment was begun.

In Fig. II the blood pressure readings are presented in graphic form. No significant change in blood pressure occurred during the 4 weeks of observation after the administration of anti-kidney serum in the group which did not receive cortisone (Group I). In the second group, which received cortisone, a moderate rise in blood pressure occurred during a similar period of time. These changes were in the same direction but less striking than had been observed previously in nephritic rats given DCA in comparable dosage.(5) In the group of adrenalectomized rats given cortisone (Group III), hypertension appeared and was of a much more impressive degree than in Group II.

In Table I the results of the chemical determinations are tabulated. Comparison of the values obtained in the first and second groups shows no significant differences with the possible exception of the serum cholesterol, which was somewhat more elevated in the group receiving cortisone. In the adrenalectomized group (III) given cortisone, the highest value for serum sodium was obtained.

The averages and range of weights for the various organs are presented in Table II. Because of the varying size of the animals and because the groups were comprised of varying numbers of males and females, interpretation of the results is difficult. However, cardiac and renal hypertrophy was not observed in the cortisone treated groups (II and III) in the degree previously noted with DCA.(5) On the other hand, the well known atrophy of thymus and of adrenals was apparent in the cortisone injected animals.

In Table II the data pertaining to histological examination of the kidneys is included. The majority of animals in all 3 groups showed evidence of nephritis, involving glomerular, tubular and interstitial elements. Thus, cortisone failed to prevent the establishment of nephritis caused by anti-kidney serum. A comparison of the severity of the nephritis in the different groups is hazardous because of the small number of animals employed and because this form of renal damage exhibits considerable variation from animal to animal.

TABLE I.
Results of Chemical Determinations.

Group	I	II	II
Adrenals	Intact	Intact	Out
Regimen	AKS	Cortisone and AKS	AKS and Cortisone
Serum sodium, mEq/L	136.4*	139.2*	143.5†
Serum CO_2 content, mEq/L	23.0*	24.8*	—
Serum chlorides, mEq/L	98.0*	98.2*	—
Serum sugar, mg/100 cc	174.0*	164.0*	—
Serum urea nitrogen, mg/100 cc	22.0*	24*	22†
Serum cholesterol, mg/100 cc	282*	330*	—

AKS = Rabbit anti-rat kidney serum.
* Results based on pooled sera from all animals.
† Results based on average of individual determinations on 6 animals.

TABLE II.
Body and Organ Weights, Incidence of Nephritis.

Group	I	II	III
Adrenals	Intact	Intact	Out
Regimen	AKS	Cortisone and AKS	AKS and Cortisone
No. of rats in group	8	8	7
No. of ♂/♀	4/4	5/3	5/2
Body wt at sacrifice (g)			
Avg	225	210	162
Range	170-346	152-265	145-179
Kidney wt (g)			
Avg	2.71	2.76	2.46
Range	1.95-3.36	1.94-3.68	1.50-4.24
No. of animals showing nephritis	7/7†	5/6†	5/7
Heart wt (g)			
Avg	.89	.91	.82
Range	.77-.98	.75-1.13	.66-1.18
Thymus wt (mg)			
Avg	141	46	49*
Range	105-173	21-87	38-61
Adrenals wt (mg)			
Avg	52.8	31.1	
Range	42.8-67.6	18-44.4	

AKS = Rabbit anti-rat kidney serum.
* Avg of 6 animals.
† Tissues of remaining animals lost.

The lesions appeared to be of no greater severity among the two hypertensive groups (II and III) than among the normotensive group.

Dr. Philip E. Smith, who was kind enough to examine the pituitary glands of these rats for evidence of hyalinization of basophilic cells as described by Crooke in Cushings Syndrome, reported no significant differences between control and cortisone injected animals. However, he has emphasized that the histological differentiation of rat pituitary gland is not wholly satisfactory.

Discussion. Cortisone has been reported to cause striking remissions in certain diseases in which antigen-antibody reactions are believed to play a role. The present study was designed to investigate whether the injection of

this steroid might interfere with the development of a cytotoxic serum nephritis, the mechanism for which is likewise presumed to depend upon some form of sensitization. The results indicate that the administration of cortisone, even when given prior to the injection of antikidney serum, as in Group II, failed to prevent the development of nephritis. Since this form of nephritis represents, at least initially, the result of the introduction of preformed antibodies, these findings do not exclude the possibility that cortisone may influence the mechanisms involved in active antibody production.

In experiments with nephritic rats previously reported,(5) desoxycorticosterone acetate (DCA), when injected daily in doses of 2.5 mg over a period of weeks, produced striking hypertension. The present study indicates that cortisone, a steroid which differs from DCA in many of its physiological properties, has an effect upon the blood pressure qualitatively similar to DCA. However, in the animals with intact adrenal glands, the hypertension produced by cortisone was far less impressive than that seen previously with DCA, particularly so since in the present study a considerably higher sodium chloride intake was given. On the other hand, in the adrenalectomized rat given cortisone the hypertension is striking, and suggests the possibility that in the intact animals, the presence of other adrenal steroids tends to counteract the pressor effect of this steroid. The development of hypertension during cortisone administration in the adrenalectomized rat with renal damage is in keeping with the previous work of Guadino.(7) Working with rats made hypertensive by a combination of unilateral nephrectomy and wrapping the remaining kidney with gauze and collodion, he observed a fall in blood pressure to follow adrenalectomy. Subsequently, cortisone injections led to a reappearance of the hypertension.

In the rats currently reported, the striking hypertension which appeared in the cortisone treated adrenalectomized group could not be correlated with a greater degree of nephritis in these animals inasmuch as renal lesions of comparable severity were observed in the other two groups.

Summary. 1. The administration of cortisone did not prevent the development of experimental cytotoxic serum nephritis in the rat.

2. Moderate hypertension developed in nephritic rats with intact adrenal glands when injected with cortisone, whereas striking hypertension appeared in adrenalectomized nephritic rats similarly treated.

3. The nephritic rats rendered hypertensive by the administration of cortisone presented no greater histological evidence of renal damage than did normotensive control nephritic animals.

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