

STUDIES OF 17-HYDROXYCORTICOSTEROIDS. V. RESPONSES OF 17-HYDROXYCORTICOSTEROIDS, EOSINOPHILS, AND GLUCOSE TO ACTH AND EPINEPHRINE¹

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The belief has been rather widespread, because of the similarities between the responses elicited by epinephrine and ACTH, that these agents produce many of their responses by similar mechanisms. There is considerable evidence which tends to support this viewpoint: 1) Both are considered to be essential agents for adequate response of the organism to stressful situations (1-5); 2) both produce eosinopenia, lymphopenia, and depletion of adrenal ascorbic acid and cholesterol (5-10); 3) several authors have presented data indicating that epinephrine stimulation of the anterior pituitary results in release of ACTH (11-13). On the other hand, certain differences between effects of epinephrine and ACTH have been demonstrated clearly: 1) The hyperglycemic responses to these two stimulating agents are produced by different mechanisms (14, 15); 2) recent publications have suggested that this is true also of the eosinopenic response (6, 16-18); 3) the administration of epinephrine produces no increased release of 17-OH-corticosteroid hormones from the adrenal cortex such as that produced by the administration of ACTH (6, 19-21).

The apparent discrepancies among published data concerning the mechanisms of responses to these two stimulating agents have prompted further study of this problem. In the present report data are presented comparing the responses of eosinophils, blood glucose, and plasma 17-OH-corticosteroids to ACTH and to epinephrine.

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MATERIALS AND METHODS

The subjects employed in this study were 40 normal children and 116 children with the following disorders: 6 with congenital adrenal hyperplasia; 25 with rheumatic disease (pre- or post-hormone therapy); 29 with mental retardation excluding mongolism and convulsive disorders; and 56 with convulsive disorders both treated and non-treated. Responses of eosinophils, glucose, and plasma 17-OH-corticosteroids to the subcutaneous injection of 0.01 mgm. epinephrine-HCl per Kg. or the intramuscular injection of 25 I.U. ACTH⁴ were studied. Eosinophils were determined by the method of Randolph (22), glucose by the method of Nelson (23), and plasma 17-OH-corticosteroids by the method of Nelson and Samuels (24). Total eosinophil counts and blood glucose levels were determined at 0, 1, 2, and 4 hours. These responses are expressed as maximum per cent decrease in the eosinophil count and maximum per cent increase in glucose concentration. The 17-OH-corticosteroid values were measured at 0 and 2 hours (21).

OBSERVATIONS

Control values in the different groups

In Table I are shown the mean fasting morning values for eosinophils, glucose, and 17-OH-corticosteroids in each of the five groups of children. As shown by these data, the children with congenital adrenal hyperplasia had significantly higher eosinophil counts and lower glucose and 17-OH-corticosteroid concentrations than normal children. In patients with rheumatic disease the eosinophil counts were apparently less than normal although this difference was not significant at the 2 per cent level; their glucose and 17-OH-corticosteroid concentrations did not differ from normal. In the patients with simple mental retardation, although the mean eosinophil counts and 17-OH-corticosteroid concentrations were

⁴ ACTHAR furnished through the courtesy of the Armour Laboratories.

TABLE I

Initial fasting eosinophil counts and concentrations of glucose and 17-OH-corticosteroids in different groups of patients

Group	Eosinophils				Glucose				17-OH-corticosteroids			
	No. tests	Mean	SEM	P (vs. Normal)	No. tests	Mean	SEM	P (vs. Normal)	No. tests	Mean	SEM	P (vs. Normal)
Normal	56	187	±15.6	—	55	76	±2.6	—	40	12.0	±1.29	—
Congenital adrenal hyperplasia	70	265	±19.8	<.01	48	63	±2.2	<.01	18	2.7	±0.82	<.01
Rheumatic disease	59	138	±15.1	<.05 >.02	58	71	±1.9	>.05	62	14.5	±2.56	>.05
Mental retardation	29	190	±23.4	>.05	29	90	±2.2	<.01	29	8.8	±1.02	>.05
Convulsive disorder	57	188	±19.1	>.05	59	80	±1.5	>.05	52	11.1	±1.28	>.05

TABLE II

Comparison of responses of eosinophils, glucose, and 17-OH-corticosteroids to ACTH and epinephrine

Group	Eosinophils					Glucose					17-OH-corticosteroids				
	No. pts.	No. tests	Response (% decrease)			No. pts.	No. tests	Response (% increase)			No. pts.	No. tests	Response (increase µg. %)		
			Mean	SEM	P (vs. Normal)			Mean	SEM	P (vs. Normal)			Mean	SEM	P (vs. Normal)
Response to ACTH															
Normal	40	40	52	±6.6	—	40	40	12	±2.4	—	40	40	17.8	±1.76	—
Congenital adrenal hyperplasia	6	46	25	±4.5	<.01	6	32	14	±3.2	>.05	6	18	0	±0.37	<.01
Rheumatic disease	17	36	49	±7.5	>.05	15	35	14	±3.3	>.05	17	35	22.7	±4.19	>.05
Mental retardation	24	24	62	±6.3	>.05	24	24	5	±2.3	<.05 >.02	25	25	8.6	±1.63	<.01
Convulsive disorder	46	46	55	±10.9	>.05	46	46	8	±3.9	>.05	42	42	9.7	±2.80	<.02 >.01
Response to epinephrine															
Normal	20	20	54	±6.4	—	22	22	55	±6.7	—	20	20	-0.3	±1.83	—
Congenital adrenal hyperplasia	6	24	57	±4.6	>.05	6	16	86	±11.8	<.05 >.02	6	12	-0.7	±0.74	>.05
Rheumatic disease	15	26	41	±11.8	>.05	15	26	50	±7.6	>.05	15	27	0.5	±2.46	>.05
Mental retardation	5	5	64	±23.5	>.05	5	5	66	±9.8	>.05	—	—	—	—	—
Convulsive disorder	10	10	58	±10.0	>.05	10	10	53	±7.6	>.05	10	10	1.2	±1.76	>.05

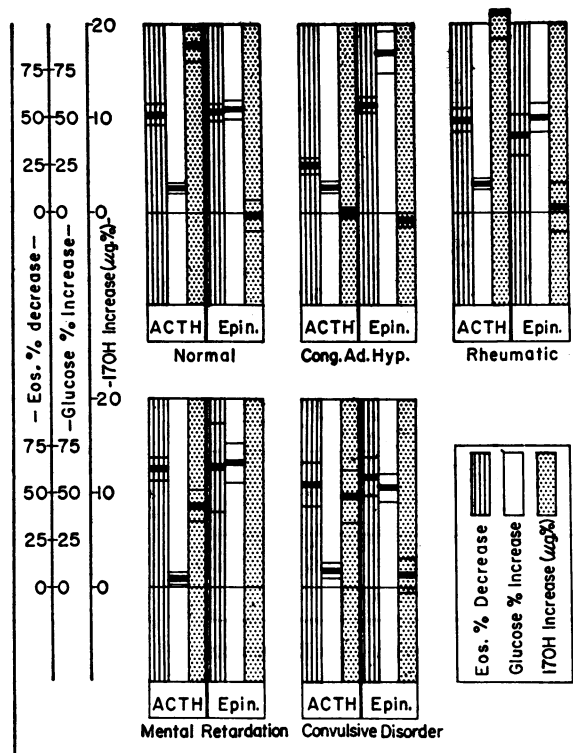


FIG. 1. MAGNITUDE OF RESPONSES IN THE DIFFERENT GROUPS

normal, the blood glucose concentrations were significantly higher than normal. The groups of patients with convulsive disorders did not differ from the normal group with respect to any of the variables studied.

Table II shows the responses of eosinophils, glucose, and 17-OH-corticosteroids to ACTH and to epinephrine in the various groups of subjects. Eosinophil responses to ACTH did not differ significantly from those of the controls in any group except that of congenital adrenal hyperplasia. In patients with this condition the eosinopenia induced by ACTH was significantly less than normal (25 per cent *vs.* 52 per cent depletion). On the other hand, the eosinopenic response to epinephrine did not differ significantly in any of the groups studied. In the congenital adrenal hyperplasia group, statistical comparison demonstrates a significant difference in the same individuals between the eosinopenic responses to ACTH and to epinephrine (ACTH: -25 ± 4.5 per cent; epinephrine: -57 ± 4.6 per cent; $p < .01$).

The magnitude of the hyperglycemic response

to a single injection of ACTH was small as compared with that to epinephrine. Among the groups studied only that with mental retardation had an hyperglycemic response to ACTH significantly less than that of the control group. In contrast, the hyperglycemic response to epinephrine was normal in this group as it was in all other groups except that with congenital adrenal hyperplasia; in the latter, this response was significantly greater than normal.

The 17-OH-corticosteroid responses to ACTH were abnormal in three of the study groups: congenital adrenal hyperplasia, mental retardation, and convulsive disorder. In the congenital adrenal hyperplasia group the initial plasma steroid levels were very low and no elevation occurred in response to ACTH. In contrast, the mental retardation and convulsive disorder groups had normal initial steroid levels but their responses to ACTH were intermediate between those of the normal and the congenital adrenal hyperplasia groups, indicating impaired but not absent adrenal cortical function. In no group was there any steroid response to epinephrine.

Figure 1 illustrates graphically the data of Table II. In the normal group eosinopenic responses to ACTH and to epinephrine were essentially the same; hyperglycemic response to epinephrine was considerably greater than that to

TABLE III

Comparison of hyperglycemic and 17-OH-corticosteroid responses to 25 I.U. ACTH *vs.* 100 I.U. ACTH

Pt.	Glucose (% increase)		17-OH-corticosteroid (ug. % increase)	
	ACTH		ACTH	
	25 I.U.	100 I.U.	25 I.U.	100 I.U.
T. G.	40	38	16.3	19.9
V. M.	4	9	2.4	27.6
L. W.	4	28	18.4	12.5
Z. G.	40	74	14.0	37.2
P. C.	24	18	39.2	66.1
C. B.	29	14	30.0	33.1
D. S.	37	14	37.0	66.4
T. G.	48	40	19.2	22.8
L. H.	8	11	18.4	26.7
R. S.	33	37	-11.5	27.1
C. E.	3	3	1.3	13.9
Mean	25	26	16.8	32.1
SEM	± 5.1	± 6.0	± 4.62	± 5.55
P (25 <i>vs.</i> 100 ACTH)	>0.05		<0.05 >0.02	

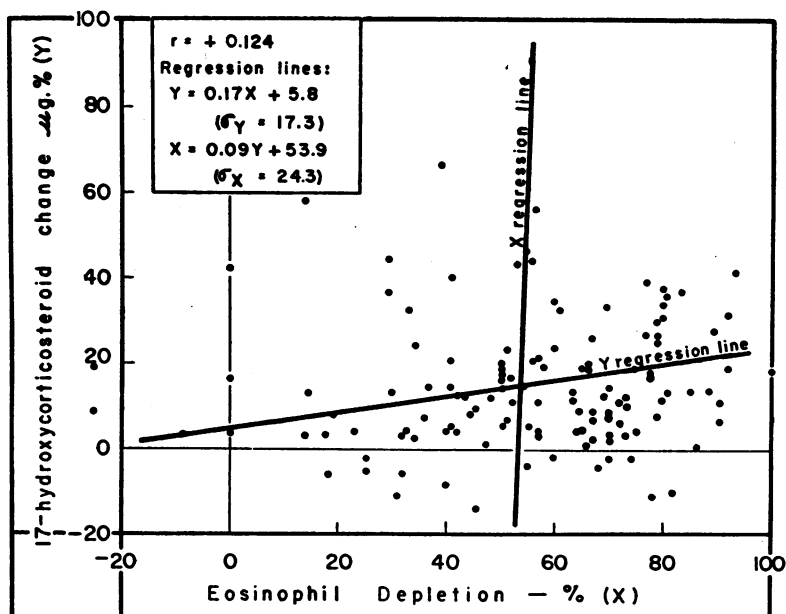


FIG. 2. COMPARISON OF EOSINOPHIL AND 17-OH-CORTICOSTEROID RESPONSES TO ACTH

ACTH; and steroid response to ACTH was of considerable magnitude whereas there was no steroid response to epinephrine. In the congenital adrenal hyperplasia group the pattern of these responses differed in that the eosinophil response to ACTH was less, the glucose response to epinephrine was greater and there was no steroid response to ACTH. Responses in the rheumatic group were comparable to those in the control group. The mental retardation group showed decreased glucose and steroid responses to ACTH in comparison with the normal group. In the convulsive disorder group the decreased steroid response to ACTH was the only response which differed from normal. Throughout all groups the glucose response to epinephrine was considerably greater than that to ACTH.

Table III compares the individual responses of glucose and of 17-OH-corticosteroids to 25 I.U. and to 100 I.U. ACTH in 11 patients. Whereas 100 I.U. ACTH produced a greater magnitude of steroid response than did 25 I.U. ACTH (32.1 *vs.* 16.8 $\mu\text{g.}$ per cent) it did not produce any greater hyperglycemic response. Furthermore, there was no apparent correlation between the magnitudes of steroid and glucose responses to ACTH.

Figure 2 shows as a scattergram the comparison of simultaneous eosinopenic and steroid responses to ACTH in 128 individuals from all

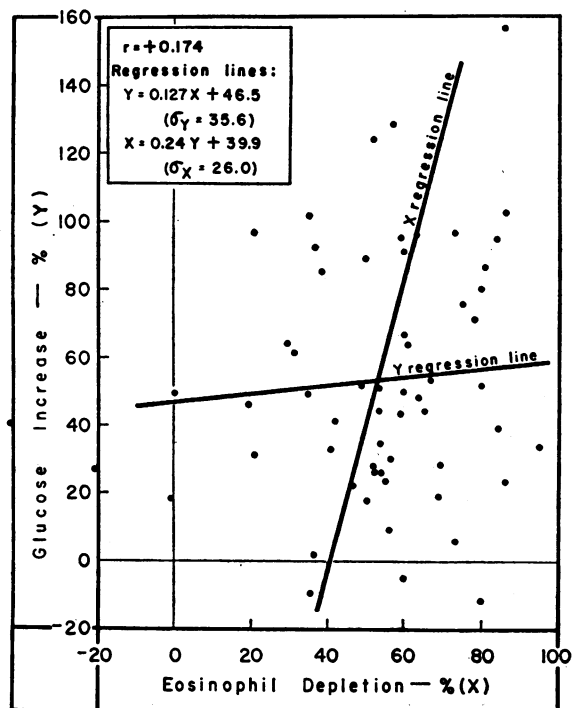


FIG. 3. COMPARISON OF EOSINOPHIL AND GLUCOSE RESPONSES TO EPINEPHRINE

groups except congenital adrenal hyperplasia. For each subject the change in steroid concentration ($\mu\text{g. per cent}$) observed two hours after the administration of ACTH was plotted against the maximum per cent decrease in eosinophil count in a four-hour period. The correlation coefficient ($\sqrt{r} = +0.124$) indicates that no significant correlation existed.

Figure 3 compares in a similar manner the simultaneous eosinopenic and hyperglycemic responses to epinephrine in 61 children. In this figure the maximum per cent decrease in eosinophil count was plotted against the maximum per cent increase in glucose concentration observed in each subject. Again, the "r" value (+0.174) indicates no significant correlation between these two variables.

Comparison of the ACTH-glucose response with the other responses to ACTH was not made because of the small magnitude of this response. Since no steroid response to epinephrine occurred, no comparison was made with the other responses to epinephrine.

DISCUSSION

It appears clear that the total circulating eosinophil count is influenced by adrenal cortical hormone. Eosinopenia is seen in patients with Cushing's disease (25) and in patients treated with ACTH or adrenal steroids. Eosinophilia generally exists in the adrenalectomized animal and in patients with Addison's disease (26, 27). Also, as shown here, eosinophilia of mild degree exists in children with congenital adrenal hyperplasia. These patients have a "segmental" adrenal insufficiency as shown by their inability to produce appreciable quantities of 17-OH-corticosteroids, the principal adrenal cortical hormones, even in response to large doses of ACTH.

The responses of eosinophils to epinephrine and to ACTH have been used clinically as criteria of adrenal cortical function. However, there now is considerable evidence to support the belief that the epinephrine-eosinophil response is not a valid criterion of this function (6, 7, 16, 17, 20, 28). Likewise, it has been suggested (6) that the ACTH-eosinophil response need not be mediated by an increased production of adrenal steroids. These points both are well substanti-

ated by data presented here which show that: 1) There is no steroid response to epinephrine in any group of patients despite adequate eosinophil responses in all groups; 2) in patients with congenital adrenal hyperplasia there is some, albeit inadequate, eosinopenic response to ACTH without any concurrent steroid response; and 3) there is no significant correlation between the magnitude of eosinophil and of steroid responses to either ACTH or epinephrine. Thus, it seems that the eosinopenia produced by either epinephrine or ACTH is not related quantitatively to 17-OH-corticosteroid release by the adrenal cortex. This eosinopenia may be associated with the release of some other adrenal steroid. In addition, epinephrine induced eosinopenia may be related to some function of epinephrine other than pituitary adrenal cortical stimulation. There is evidence to suggest that it may be the result of a synergistic action between epinephrine and adrenal cortical hormones (18).

A direct relationship between the adrenal cortex and carbohydrate metabolism is known to exist. In patients with Addison's disease and in adrenalectomized dogs, episodes of hypoglycemia occur frequently. Conversely, patients with Cushing's disease often have hyperglycemia and diabetic glucose tolerance curves. Furthermore, "steroid diabetes" has been produced in animals (15) and in human subjects (29). Information such as this has led to attempts to evaluate the status of adrenal cortical function on the basis of the alterations in blood glucose concentration resulting from the administration of ACTH. Evaluation of adrenal cortical function by the hyperglycemic response to ACTH has been made: 1) In patients with hypoglycemia (30, 31); 2) with continued ACTH administration (29, 32, 33) and; 3) in terms of the effect of ACTH on the glucose tolerance curve (29, 30). Little mention has been made of the hyperglycemic response to a single injection of ACTH. The studies reported here show that normally only a small response occurs and suggest that this test is of no practical value. The significance of the poor hyperglycemic response to ACTH seen in the group of patients with mental retardation is unknown.

It has been suggested (34) that adrenal cortical hormones participate in the alterations of

carbohydrate metabolism following the injection of epinephrine. The adequate hyperglycemic response to epinephrine without any 17-OH-corticosteroid response, observed in all the groups studied, neither supports nor refutes this concept. Even though the hyperglycemic response to epinephrine is not mediated by an increased plasma 17-OH-corticosteroid level the possibility exists that these steroids may act synergistically with the administered epinephrine in producing this hyperglycemic response in a manner similar to that postulated for the eosinopenic response to epinephrine (18). The consideration that identical synergistic mechanisms are involved has little support, since no correlation exists between the eosinopenic and hyperglycemic responses to epinephrine (Figure 3). Although the concept of an epinephrine-17-OH-corticosteroid synergism is weakened somewhat by the observations of ample hyperglycemic and eosinopenic responses to epinephrine despite very low plasma 17-OH-corticosteroid concentrations in the congenital adrenal hyperplasia group, it is not invalidated by these observations.

Responses of glucose, eosinophils and 17-OH-corticosteroids all have been used as criteria of adrenal cortical function. Since there is no significant correlation among the three responses and since the 17-OH-corticosteroid response measures adrenal cortical secretory function in terms of the major steroids produced, the latter test appears to be the one of preference. However, the clinical application of this steroid response test has certain limitations (19) and the other response tests, particularly the ACTH-eosinophil response, still have clinical values—at least as screening tests.

SUMMARY

1. Fasting levels of eosinophils, glucose and 17-OH-corticosteroids, and their responses to ACTH and to epinephrine were compared in different groups of children. Certain differences were noted among the groups studied.

2. No correlation was found between the magnitude of: 1) Eosinopenic and 17-OH-corticosteroid responses to ACTH or ; 2) eosinopenic and hyperglycemic responses to epinephrine.

3. The hyperglycemic response to ACTH was slight.

4. No 17-OH-corticosteroid response to epinephrine was found.

5. The 17-OH-corticosteroid response to ACTH is considered the most valid of the tests compared.

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