in control animals which received saline injections. (c) Gas pockets in a group of adrenalectomized mice were compared with those in intact, untreated controls. The cobalt injections produced an increase in pO_2 of the gas pocket which appeared the first day after beginning treatment. The adrenalectomized mice showed no difference from their controls in gas pocket pO_2. Since decreased pO_2 was not observed, it was concluded that the protection of the two treatments against oxygen toxicity must be due to other factors.

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Abolition by Hypophysectomy of the Anticortisol Action of Desoxycorticosterone. (22872)

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Numerous experiments have shown that there is an antagonism between glucocorticoids and mineralocorticoids, as regards their effects upon inflammation, in that the inhibitory action of the former can be blocked by the latter, under suitable experimental conditions. However, these opposing effects appear to be exerted through different mechanisms. The anti-inflammatory action is presumably direct, since it occurs even topically, at the site where glucocorticoid (*e.g.* cortisol) is applied, while the contrary effect of mineralocorticoids (*e.g.* desoxycorticosterone) is probably indirect because it can be obtained only by systemic treatment. An essential difference in modes of action of these two types of corticoids is also suggested by the observation that hypophysectomy does not interfere with most of the classic glucocorticoid effects, but does prevent many of the morbid lesions characteristic of mineralocorticoid overdosage, such as nephrosclerosis, periarteritis nodosa and hypertension(1,2,3,4,5,6).

In view of these facts it appeared of interest to determine whether, even in the absence of the hypophysis, systemic treatment with a mineralocorticoid would exert pro-inflammatory actions in itself, or block the anti-inflammatory effect of a glucocorticoid. It had been demonstrated that the "granuloma-pouch" technic lends itself well for quantitative assessment of inflammation in hypophysectomized rats(7) and, therefore, we used this test object for our studies.

Materials and technics. Eighty female Sprague-Dawley rats, with mean initial body-weight of 160 g (range: 150-168 g), were subdivided into 7 groups, as indicated in Table I. On the first day, a granuloma-pouch was produced as follows: (1) injection

TABLE I. Somatic and Organ-Weights in the Hypophysectomized Rat.

Group	Treatment	No. of animals	Final body wt, g	Wt loss, %	Exudate, ml	Granuloma pouch, mg	Thymus, mg	Spleen, mg
1	Hyp-X	10	138 ± 4.9	14	18.7 ± 1.8	2442 ± 246	149 ± 16	290 ± 16
2	" + COL-Ac	10	114 ± 1.5	29	8 ± 1.2	1357 ± 115	28 ± 1.6	179 ± 9.1
3	" + DOC-Ac	10	137 ± 4.4	16	18.8 ± 1.8	2438 ± 198	117 ± 18	262 ± 18
4	Hyp-X + COL-Ac + DOC-Ac	10	114 ± 1.8	29	8.6 ± 1.3	1408 ± 113	13 ± 5.4	181 ± 8.2
5	Hyp-X + Adr-X + COL-Ac	13	117 ± 1.4	27	4 ± .74	933 ± 104	216 ± 2.5	161 ± 14
6	Hyp-X + Adr-X + DOC-Ac	14	138 ± 3	15	18.5 ± .7	2712 ± 179	128 ± 14	279 ± 15
7	Hyp-X + Adr-X + COL-Ac + DOC-Ac	13	123 ± 1.3	23	7.1 ± 1.1	1196 ± 160	28 ± 2.2	191 ± 7.7

through a No. 27 gauge needle of 25 ml of air into subcutaneous tissue underneath the shaved dorsal skin, to form a single cavity. (2) without withdrawing the needle 1 ml of 1% croton-oil solution (in corn oil) was injected into the air sac thus created. Forty-eight hours later the animals of all groups were hypophysectomized through the parapharyngeal route and those of Groups 5-7 were bilaterally adrenalectomized through the lumbar route. At that same time, treatment was begun with cortisol acetate (COL-Ac) with 400 μg/day alone or with desoxycorticosterone acetate (DOC-Ac) at daily dose of 100 μg, both compounds being injected subcutaneously in the form of microcrystal suspensions in 0.2 ml of water. All animals were allowed free access to Purina Fox Chow and Pablum. Four rats each in Groups 1 and 3, one rat each in Groups 4 and 5 and three rats in Group 6 died during the experiment. All the remaining animals were killed on 12th day after initiation of hormone treatment. Immediately afterwards the exudate was measured by aspiration into a graduated syringe, while the granulomatous walls of the pouches and the organs listed in Table I were dissected and fixed in Susa solution for subsequent weighing.

Results. Table I summarizes our principal results. Although all animals lost some *body-weight,* those both adrenalectomized and non-adrenalectomized and given COL-Ac exhibited the most pronounced catabolism. This weight loss was not inhibited by concurrent treatment with DOC-Ac, either in the merely hypophysectomized or in the hypophysectomized-adrenalectomized animals (Groups 4 and 7). *Exudate formation* and weights of *granuloma-pouches* were significantly depressed in all groups receiving COL-Ac. This anti-inflammatory effect was more pronounced in animals which were both hypophysectomized and adrenalectomized (Group 5) than in those merely hypophysectomized (Group 2), since the apparent difference in exudate formation ($P<0.02$), and in weight of granuloma-pouches ($P<0.05$) was significant. It is doubtful, however, whether this small difference should be ascribed to the anticortical effect of endogenous mineralocorticoids secreted by adrenals of the merely hypophysectomized rats; possibly the animals subjected to the double operation were just too damaged to respond normally. In any event, concurrent treatment with DOC-Ac did not significantly inhibit the anti-inflammatory action of COL-Ac, either in the merely hypophysectomized or in the hypophysectomized and adrenalectomized rats. Similarly, the *thymolytic* and *splenolytic* effects of COL-Ac were manifest in all groups, irrespective of whether DOC-Ac had or had not been given simultaneously. The observation that the thymus appears to be even smaller after combined treatment with COL-Ac and DOC-Ac in Group 4, than it is following administration of the former hormone alone, in Group 2, is probably meaningless. It must be kept in mind that it becomes virtually impossible to

dissect the thymus accurately for weighing if this organ becomes so atrophic that its weight falls below 30 mg. DOC-Ac given by itself did not exert any stimulating effect, either upon the indicators of inflammation or upon the lymphatic organs (Groups 3 and 6).

Discussion. The anticatabolic, pro-inflammatory, thymotrophic and splenotrophic actions of DOC-Ac are never conspicuous in intact animals, but all these effects are always very pronounced (at dose-levels used here) when DOC-Ac is given to adrenalectomized rats maintained with COL-Ac. Presumably the adrenal of the intact animal supplies an optimal amount of mineralocorticoid already so that additional DOC-Ac treatment does not produce any manifest effect(8). This is probably also the reason why the anticortisol actions of aldosterone are likewise much more evident in adrenalectomized than in intact rats(9). Hypophysectomy does not totally abolish mineralocorticoid secretion by the adrenals; hence, it might have been supposed that the inactivity of DOC-Ac in our hypophysectomized rats was likewise due to the fact that they possess an adequate supply of endogenous mineralocorticoids. However, as we have seen, DOC-Ac does not exert any evident anticortisol action, even in simultaneously hypophysectomized and adrenalectomized rats maintained on COL-Ac. It is much more probable that some pituitary factor is necessary for the manifestation of the anticortisol actions of DOC-Ac.

It had been demonstrated previously that STH does not exert any of its characteristic actions (upon somatic growth, thymicolymphatic development, inflammation) in adrenalectomized rats maintained exclusively on COL-Ac, unless mineralocorticoid treatment is given. Conversely, overdosage with DOC-Ac fails to produce nephrosclerosis, periarteritis and hypertension, in the absence of the pituitary, unless adequate maintenance therapy with STH-containing pituitary extracts, or hypophyseal implants is provided (10). It remains to be seen whether STH is the hypophyseal factor necessary for the obtention by mineralocorticoids of anticortisol actions, but the present experiments suggest to us that, not only the damaging effects of DOC-Ac upon the kidney and the cardiovascular system, but even its ability to antagonize the catabolic antiphlogistic, thymolytic and splenolytic effects of cortisol is dependent upon the hypophysis.

Summary. Hypophysectomy, with or without adrenalectomy, abolishes the anticortisol effects (upon catabolism inflammation, thymolysis and splenolysis) of desoxycorticosterone acetate, seen in the adrenalectomized rat. Apparently, the anticortisol actions of mineralocorticoids are indirect, and depend upon some hypophyseal conditioning factor.

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