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LETTERS TO THE EDITOR

Low Dose ACTH Test—A Word of Caution to the Word of Caution: When and How to Use It[a]

To the editor:

In 1991 we introduced the low dose ACTH test (1). Since then, numerous papers (2–6) have confirmed our data. Lately, two contradictory letters in *JCEM* challenged the validity of the test. The first (7), based on feelings rather than facts, suggests that even 1 μg of ACTH might be too high a dose for a physiologic stimulation of the adrenal. The second (8) suggests (based on one case) that 1 μg may in some cases or situations be too low a dose for this purpose.

It is difficult to argue with the first letter (7), as no facts are given. However, while most investigators still use 250 μg ACTH as the adrenal stimulating dose, to speculate that 1:250 that amount is still too high seems speculative. The second letter (8) is based on a bizarre case in which subnormal response to the low dose ACTH test was noticed, but also no response was noticed to CRH, or to insulin challenge. A repeated low dose ACTH test was normal (though no data are given!).

The best explanation in our view to these results might be that, in the first low dose ACTH test, not all of the dose was administered intravenously. As this test was not done by the authors themselves, this possibility will probably never be confirmed or denied. However, it is very important to emphasize that, unlike the high dose ACTH test, where the dose is well above normal, in the low dose test all of the hormone must be introduced intravenously to get the normal response. In case of doubt the test should be repeated. We do agree with the authors that the low dose ACTH test should be used as a screening test, and another confirmatory test (we advocate the metyrapone test) should be done before lifetime steroid treatment is given. However, if the low dose ACTH test is normal, no further tests to exclude adrenal insufficiency are needed. The only cases in which the low dose ACTH test is of very little value are those of newly onset pituitary insufficiency (pituitary surgery or apoplexy) in which the adrenal response, even to low doses of ACTH is still preserved.

We would like also to reemphasize that 1–24 ACTH can be kept refrigerated in glass tubes at a concentration of 5 μg/mL for up to 4 months (1). This makes the test much easier, as only one dilution is needed immediately before injection.

We now have experience with more than 100 patients, in all of whom a normal response (>18 μg/100mL cortisol level 30 min after injection) was achieved with the 1 μg ACTH test. In summary, we have two words of caution about the low dose ACTH test: be sure that you inject the whole dose intravenously, and be sure that you do not test a patient with very recent pituitary insufficiency.

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Activity of the Renin-Angiotensin-Aldosterone Axis is Dependent on the Occurrence of Edema in Growth Hormone(GH)-Deficient Adults Treated with GH[b]

To the editor:

While the antinatriuretic properties of growth hormone (GH) have been known for more than 40 yr, the mechanism underlying this effect and, in particular, the role of the renin-angiotensin-aldosterone(RAA) axis as a mediator of GH-induced sodium retention remain contentious. While early studies using supraphysiologic doses of GH in normal subjects (1) and GH-deficient adults (2) demonstrated both acute and chronic activation of the RAA axis, a recent report by Hoffman *et al.* (3) showed no acute increase in aldosterone secretion in GH-deficient adults after 7 days treatment with physiologic doses (0.04U/kg/d) of GH. We report our examination of the RAA axis during chronic, physiologic GH administration.

In a double-blind, placebo-controlled trial we examined the impact of 6 months GH treatment on aldosterone and plasma renin activity (PRA) in 10 GH-deficient adults (aged 37.9 ± 3.6 yr, mean ± SEM), diagnosed on the basis of a peak GH response of less than 10 mU/L after insulin-induced hypoglycemia (n = 9) or L-Dopa (n = 1). The study was approved by the local ethics committee, and all patients gave written, informed consent.

Following treatment with GH at a dose of 0.125 U/kg/week for the first week and 0.25 U/kg/week thereafter, 5 patients developed symptoms of fluid retention in the form of edema or arthralgia. This resolved spontaneously in 1 case and required a 25% reduction in GH dose in the remainder. Total body water, measured by bioelectrical impedance analysis, increased by 3.3 ± 1.6 l ($P < 0.05$). There was no significant change in body weight, blood pressure, or serum electrolytes. Similar to the data of Hoffman *et al.* (3) we demonstrated no significant change in upright aldosterone or PRA levels in the total group. However, when those patients with and without edema were compared, there was a trend for aldosterone and PRA levels to increase in those patients who developed edema and to fall in those who did not (Fig. 1). The failure of these changes to achieve statistical significance is likely the result of the small numbers within each subgroup.

These data indicate that the lack of stimulation of the RAA axis seen in the acute setting following physiologic GH replacement (3) is also true of chronic GH administration. In addition, this study makes the original observation that the pattern of aldosterone and PRA response seen with GH treatment is probably dependent on the edema status of the patient. The demonstration that nonedematous GH-treated patients tended to have lower RAA activity is consistent with the hypothesis that sodium retention associated with GH is due to a direct renal tubular effect. The tendency for aldosterone and PRA levels to increase in those patients in

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