

develops concealed hostility and difficulty in demonstrating feelings of aggression to people around. Is this true and do you think that this is responsible for their depression?

DR. ZAPHIROPOULOS It is true that patients with chronic disability are likely to exhibit 'conflicts in the expression of hostility', but I do not know whether the anxiety and depression is a result of this; they are all part of the general disturbance seen in rheumatoid patients (Robinson, Kirk, Frye, and Robertson, 1972).

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**Effect of Corticotrophin and Oral Corticosteroids on nocturnally released Growth Hormone.** By R. MOTSON, D. N. GLASS, J. I. EVANS, P. HILL, J. R. DALY, and N. RUDOLF (*Clinical Research Division, Kennedy Institute of Rheumatology, West London Hospital, and Department of Psychiatry, Edinburgh University*)

Corticosteroid therapy in children is associated with dwarfism, although there is uncertainty about the mechanism of this. Chronically administered steroids can inhibit the growth hormone response to insulin-induced hypoglycaemia, but generally only after some years of therapy and without uniformity. It has not hitherto been possible to find an index of growth hormone function which was inhibited by a dose of steroids unless given for more than 2 to 3 days. It is necessary to find a more physiological index for growth hormone before one could relate levels to dose of steroids, rates of growth, or any other metabolic function.

Growth hormone release is now well documented in association with Stages 3 and 4 of slow-wave sleep (Takahashi, Kipnis, and Daughaday, 1968). This sleep-associated growth hormone release appears to be a physiological situation in which one can study growth hormone satisfactorily, and avoids the necessity for artificial stimuli such as insulin hypoglycaemia or arginine infusions which have been used for previous studies of the effect of corticosteroid therapy on growth hormone secretion. We have undertaken a systematic examination of the effects of corticosteroids on nocturnal growth hormone release, and have previously reported the suppressive effect on growth hormone release of a single injection of Depot Tetracosactrin given to normal subjects 16 hours before the onset of sleep (Glass, Evans, and Daly, 1972). Further experience now shows that this effect is not obtained if a single 80 unit injection of ACTH (Acthar gel) is given at a similar time. This dose, whilst containing at least 1 mg. of the porcine ACTH preparation, gives adrenal stimulation for a much shorter period than 1 mg. Depot Tetracosactrin. The mean peak of growth hormone was  $37.9 \pm 12.3$  S.D. in five subjects compared with  $27.4 \pm 16.0$  S.D. in the same subjects during nights when the hormone was not given; the equivalent corticosteroid values being  $7.7 \pm 1.5$  and  $6.7 \pm 2.6$  respectively. In order to investigate whether the effect of Tetracosactrin on growth hormone release was a direct one, or mediated *via* the action of the raised corticosteroid level it produced, we next examined the

effect of oral corticosteroids on nocturnal growth hormone release in a group of normal individuals: a single orally administered dose of long-acting steroid (Flucortolone) significantly suppressed the sleep associated growth hormone peaks.

#### Discussion

DR. B. M. ANSELL (*Taplow*) The team should be congratulated on this difficult work. It is now time to re-think what type of steroid to give to children and when. At this moment it is still difficult to decide and I wondered if there was an urinary method of assessing growth hormone over a 24 hour period, which would be much more practicable for a childhood study.

DR. MOTSON We have done one or two estimations on urine growth hormone but have not been able to find a satisfactory method.

DR. A. ST. J. DIXON (*Bath*) Can I ask a question for information. Is this type seen in growing children?

DR. MOTSON Yes, sleep associated growth hormone release occurs in children from 12 weeks onwards (Vigneri and D'Agata, 1971).

DR. A. ST. J. DIXON (*Bath*) And another question for elucidation. Do you feel that this is applicable to the minimizing of prednisolone damage to the collagen tissues of the body such as the bruising and the thinning of the skin and osteoporosis. Do you feel that the suppression of growth hormone is partly to blame for this?

DR. MOTSON I do not think I should go so far as to say that, since other anabolic hormones may also be suppressed by corticosteroid therapy.

DR. J. N. GLICK (*London*) Have you done any measurements on people who have had intermittent steroids?

DR. MOTSON No, but two subjects whose growth hormone was suppressed by corticosteroids had a good growth hormone rise the following night.

DR. A. ST. J. DIXON (*Bath*) What do you feel about long-acting depot preparations of steroids? I have the clinical impression that some of the worst cases of steroid damage to the tissues occur with this type of preparation.

DR. MOTSON There does appear to be a correlation between continuity of elevation of corticosteroids and suppression of growth hormone. If growth hormone suppression is associated with tissue damage, then very long-acting steroids may not be advantageous.

#### References

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**A Re-examination of the Hypoglycaemia-induced 'Stress' Response of the Hypothalamo-pituitary-adrenal Axis in Patients with Rheumatoid Arthritis on Long-term Adreno-corticotrophin (ACTH) Therapy.** By M. R. FLEISHER, D. N. GLASS, and J. R. DALY (*Clinical Research Division, Kennedy Institute of Rheumatology, and Department of Chemical Pathology, Charing Cross Hospital Medical School*)

There is considerable evidence that treatment with

corticosteroids over months or years, as may be required by patients with rheumatoid arthritis, leads to a suppression of the hypothalamo-pituitary-adrenal (HPA) response to stress (Daly, Myles, Bacon, Beardwell, and Savage, 1967). Bacon, Daly, Myles, and Savage (1968) and Carter and James (1970) found that treatment with ACTH caused less impairment of HPA function, although Levell, Stitch, and Noronha (1970), using lysine-vasopressin as the test substance, did not confirm this. In comparing these two forms of therapy, it is therefore desirable to resolve this question. Carter and James (1970), reporting that the HPA response to hypoglycaemic stress was less affected in ACTH-treated patients, based their conclusions concerning HPA function on the plasma corticosteroid response. Daly and Glass (1971), however, found an abnormal growth hormone response to hypoglycaemia, in addition to a slightly lower incremental rise of plasma corticosteroids in their ACTH-treated patients compared with control patients.

The response to stress of the pituitary element of the HPA axis has now been measured directly by means of a recently developed sensitive bioassay for ACTH (Chayen, Loveridge, and Daly, 1972).

In the present investigation we have extended previous studies to include measurement not only of growth hormone and of plasma corticosteroids, but also of ACTH in patients subjected to the stress of insulin hypoglycaemia. These parameters were investigated in twelve rheumatoid patients who had been treated with a gel-linked preparation of porcine ACTH for 3 to 18 years (mean 10.9 yrs); the results were compared with those from a series of rheumatoid patients of comparable age and sex who had not received either ACTH or systemic corticosteroid therapy.

The baseline values for blood glucose, plasma corticosteroid, and ACTH in the two groups were not significantly different. The degree of hypoglycaemia achieved was similar in the two groups (blood glucose  $21.2 \pm 10.4$  and  $19.9 \pm 11.5$  mg./100 ml.). The corticosteroid levels in the rheumatoid 'controls' reached a mean peak value of  $29.75 \pm 6.7$   $\mu$ g./100 ml.; in the ACTH-treated patients these peak values were lower ( $26.6 \pm 5.7$   $\mu$ g./100 ml.); this difference was not statistically significant ( $0.4 < P < 0.2$ ). The rise in plasma corticosteroid levels induced by the 'stress' (baseline-peak difference) was also similar in

both groups ( $0.2 < P < 0.1$ ). The marked depression of the growth hormone response, previously reported, was confirmed in the present study with a growth hormone rise in the control group of  $51.64 \pm 29.2$  ng./ml. and in the ACTH-treated group of  $13.84 \pm 13.3$  ng./ml. ( $P < 0.001$ ).

In addition, there was a marked impairment ( $P < 0.01$ ) in the rise in ACTH concentration in the ACTH-treated group ( $69.6 \pm 22.1$  pg./ml.) compared to the control group ( $129.2 \pm 63.4$  pg./ml.).

It seems, therefore, that the response of the HPA-axis, as measured directly by changes in the levels of ACTH and growth hormone is impaired in patients treated with gel-linked ACTH. However, the corticosteroid response to 'stress' is unimpaired, perhaps because of the known adrenocortical hyper-responsiveness to ACTH-induced by long-term ACTH therapy (Bacon and others, 1968).

#### Discussion

DR. P. J. L. HOLT (*Manchester*) Do I understand from both these papers that the growth hormone tends to be lower or just that the response, the nocturnal elevation, is lower in these patients? Secondly, is stress of some sort, such as playing games, important in the production of growth hormone? Is this a physiological necessity?

DR. FLEISHER As regards the first question, Dr. Motson was referring to the effect of more acute ACTH therapy on nocturnal growth hormone secretions, while I was referring to a more chronic change and I do not think that we can draw any comparison between the two studies. The answer to the second question, whether growth hormone response to hypoglycaemia is physiologically important or not, is not known. We do not know what the physiological function of growth hormone in adults is; we were simply using it here as a test of hypothalamo-pituitary function.

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