The Effect of Prolonged Corticotropin Therapy For Rheumatic Fever on the Exchangeable Sodium Content and Body Weight

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With the technical assistance of AARON J. BLUMBERG

Serial measurements of the body weight and the exchangeable sodium content were made in young patients with acute rheumatic fever who were being treated with large doses of corticotropin. All but one subject developed the clinical signs of hyperadrenalism. Eight of the 11 subjects showed at least a 20 per cent increase in body weight which could not be explained on the basis of the changes in exchangeable sodium content. This change in body composition is thought to be due primarily to an increase in total body fat.

The prolonged administration of corticotropin (ACTH) in therapeutic doses is known to produce the physical signs of hyperadrenalism. The increase in body weight resulting from such administration has usually been attributed in large measure to retention and redistribution of sodium and water. This explanation appears to be reasonable in adults, since a decrease in body weight and rapid excretion of sodium often follows the administration of a diuretic agent or the discontinuance of corticotropin. The "moon facies" and the "buffalo hump" observed clinically, however, suggest a more profound change in body composition. To date few studies on the effects of ACTH on fat metabolism have been reported.

In the course of a study on the immunophysicsology of rheumatic fever, it became apparent that rheumatic children and adolescents who gained weight while being treated with ACTH did not respond with diuresis when mercurial diuretics were given. The purpose of the present report is to demonstrate the marked discrepancy between the variations in the exchangeable sodium content of the body and the changes in the body weight during prolonged treatment of rheumatic fever with long-acting corticotropin (Acthar gel).

Material and Methods

Subjects. Eleven subjects, five females and six males, with the diagnosis of acute rheumatic fever were studied. Their ages ranged from 8 to 18 years, and seven patients were under 12 years of age. All subjects showed unequivocal clinical symptoms and signs of acute rheumatic activity as judged by the diagnostic criteria of Jones.

The general plan of therapy was to administer daily a single intramuscular injection of Acthar gel in a dosage of 1 to 2.5 units per lb. (2.0 to 5.7 units per Kg.) of initial body weight and to maintain this dosage until the clinical and laboratory evidences of rheumatic activity had subsided. The dosage of corticotropin was then gradually reduced, unless signs of rheumatic activity recurred, in which case an intermediate dosage was continued for a longer period until all signs of rheumatic activity had again subsided. The longest duration of continuous ACTH gel therapy was more than 90 days, and the shortest, 34 days.

All subjects were placed on a regular hospital diet and received supplemental feedings between meals as desired. All but one individual received oral supplements of potassium chloride, 1 to 2 Gm. thrice daily. Nine also received 200 to 1000 mg. of ascorbic acid daily by mouth.

Isotopes. Isotopic sodium (Na\textsuperscript{24})* was prepared

*Na\textsuperscript{24} was supplied by the Oak Ridge National Laboratory, Oak Ridge, Tenn., on allocation from the U. S. Atomic Energy Commission.
for injection in the manner previously described. The subjects were given 1.5 μc. of Na²⁴ per Kg. of body weight, contained in sterile physiologic saline solution.

Determination of Exchangeable Sodium Content (Na-e). Each subject received an intravenous injection of radioactive sodium from a calibrated syringe between 8:30 and 10 a.m. All urine voided for the next 24 hours was collected, and the Na²⁴ content of the pooled specimen was determined. A blood specimen was obtained 24 hours after the injection of Na²⁴, and the specific activity of the sodium in the serum was determined. The following formula was used to calculate the value for the exchangeable sodium content of the body:

$$Na-e = \frac{Na-i²⁴ - Na-u²⁴}{Na-s²⁴/Na-s²³}$$

$Na-e$ = quantity of exchangeable sodium in milliequivalents (mEq.).
$Na-i²⁴$ = quantity of radioisododium administered (arbitrary units).
$Na-u²⁴$ = quantity of radioisododium excreted in the pooled specimen of urine.
$Na-s²⁴$ = concentration of radioisododium in the serum at 24 hours.
$Na-s²³$ = concentration of nonradioactive sodium in the serum at 24 hours.
$Na-s²⁴/Na-s²³ = specific$ activity of the serum at 24 hours.

Preliminary studies in this laboratory revealed that the Na-e measurement was reproducible within five per cent in hospitalized subjects who were convalescing from various diseases. This finding agrees with those previously reported by Miller and Wilson. A total of 53 determinations of exchangeable sodium content were made; a minimum of three and a maximum of seven serial determinations were performed on each subject, usually at intervals of two to three weeks. Each patient was observed for a minimum of 50 days.

Measurement of Radioactivity. The radioactivity of the urine and serum specimens was determined with a well-type scintillation counter and a scaling circuit. A total of 10,000 counts were made on each sample. All determinations were corrected for decay of the isotope. The total sodium concentration in the serum was determined with a Baird flame photometer, using the lithium internal standard method.

Results (table 1)

Signs of hyperadrenalism. All subjects except one (case 9) showed obvious clinical signs of hyperadrenalism, moon face, cervical and supraclavicular fat pads (buffalo hump) and acne, while being treated with corticotropin. In case 9 some fullness of the face developed by the fourth week of corticotropin therapy, but there were no other obvious manifestations.

No relationship between the development of hyperadrenalism and the effect of corticotropin on the underlying rheumatic process was observed.

Changes in Body Weight (fig. 1). In nine of the 11 subjects the body weight increased by at least 10 per cent (cases 1 to 9). In five of these individuals (cases 1, 2, 3, 5 and 6) the weight gain was more than 25 per cent of the initial value. The greatest rate of increase was observed in the individual (case 1) who received the largest daily dosage of corticotropin (5.7 units per Kg.); on the seventy-fifth and eighty-ninth day, this patient's weight was 65 per cent above the original measurement. Two subjects (cases 10 and 11), although they showed the clinical signs of Cushing's syndrome, failed to gain weight.

Although there was considerable variability, the increase in body weight appeared to be progressive and related to the dosage and the duration of therapy. There was no definite relationship between the changes in body weight and the effect of corticotropin on the rheumatic process.

Changes in Exchangeable Sodium Content (Na-e) (fig. 2). Five subjects (cases 1, 5, 6, 7, and 11) revealed at least a 10 per cent increase in the exchangeable sodium content at some time during the period of observation. In two of these individuals, this increase was observed after treatment with corticotropin was discontinued. In the other three individuals, subsequent values for exchangeable sodium content obtained while the subjects were being treated with corticotropin were equal to the baseline values, or even lower.

In the other six individuals no significant increase in the exchangeable sodium content was demonstrated during corticotropin therapy. In three instances (cases 2, 3 and 4) exchangeable sodium contents 29, 22 and 21 per cent below the initial determinations were obtained while the patients were on corticotropin therapy and while body weight was increasing.
TABLE 1—The Exchangeable Sodium Content and Body Weight During ACTH Therapy of Rheumatic Fever

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yr.)</th>
<th>Sex</th>
<th>ACTH Maximum (units)</th>
<th>Dosage Total (units)</th>
<th>Duration Therapy (day)</th>
<th>Initial Body Wt. (Kg.)</th>
<th>Initial Na-e (mEq./L.)</th>
<th>Day of Rx</th>
<th>Change in Wt. (Kg.)</th>
<th>Change in Na-e (mEq.)</th>
<th>Unexplained Change in Wt.* (% Initial Wt.)</th>
<th>Serum Sodium Concentration (mEq./L.)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>8</td>
<td>M</td>
<td>120</td>
<td>6740</td>
<td>90</td>
<td>20.9</td>
<td>1071</td>
<td>6</td>
<td>+2.7</td>
<td>+265</td>
<td>+0.8 (4)</td>
<td>137.3 (−1.3)</td>
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<tr>
<td>2</td>
<td>11</td>
<td>F</td>
<td>100</td>
<td>5870</td>
<td>80</td>
<td>18.2</td>
<td>1071</td>
<td>11</td>
<td>+0.4</td>
<td>−79</td>
<td>+0.9 (5)</td>
<td>138.2 (−1.4)</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
<td>F</td>
<td>120</td>
<td>6340</td>
<td>80</td>
<td>28.2</td>
<td>1509</td>
<td>20</td>
<td>−0.1</td>
<td>−139</td>
<td>+1.0 (4)</td>
<td>143.7 (−1.7)</td>
</tr>
<tr>
<td>4</td>
<td>11</td>
<td>M</td>
<td>65</td>
<td>2828</td>
<td>51</td>
<td>32.0</td>
<td>2043</td>
<td>33</td>
<td>+2.3</td>
<td>−425</td>
<td>+5.2 (16)</td>
<td>147.8 (−3.7)</td>
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<tr>
<td>5</td>
<td>10</td>
<td>F</td>
<td>60</td>
<td>2880</td>
<td>53</td>
<td>26.8</td>
<td>1271</td>
<td>7</td>
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<td>−66</td>
<td>+1.2 (4)</td>
<td>138.2 (−1.4)</td>
</tr>
<tr>
<td>6</td>
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<td>60</td>
<td>3540</td>
<td>64</td>
<td>29.9</td>
<td>1474</td>
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<td>−29</td>
<td>+0.8 (3)</td>
<td>134.6 (−2.2)</td>
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<tr>
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<td>2255</td>
<td>24</td>
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<td>150</td>
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<td>34</td>
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<td>139.4 (5.6)</td>
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<td></td>
<td></td>
<td>45</td>
<td>+0.1</td>
<td>−217</td>
<td>+1.7 (3)</td>
<td>−2.9</td>
</tr>
</tbody>
</table>

* Unexplained change in weight (Kg.) = change in weight (Kg.) referable to initial value – change in Na-e (mEq.)/serum sodium concentration (mEq./L.) at the time of each determination.

No relationship was observed between the variations in exchangeable sodium content and the effect of corticotropin on the rheumatic process.

Unexplained Weight Change (fig. 3). This was determined by dividing the change in Na-e by the serum sodium concentration (mEq. per L.) at the time of each determination and
EFFECT OF CORTICOTROPIN ON SODIUM CONTENT AND BODY WEIGHT

FIG. 1. Weight changes in rheumatic subjects treated with corticotropin. Abscissa shows number of days of therapy; ordinate, changes in body weight (per cent of initial value).

FIG. 2. Changes in exchangeable sodium content during therapy of rheumatic fever with corticotropin. Abscissa shows days of therapy; ordinate, change in Na-e (per cent of initial value).

FIG. 3. Unexplained weight changes in rheumatic subjects treated with corticotropin. Abscissa shows days of therapy; ordinate, change in body weight (per cent of initial body weight).

subtracting this result from the change in weight (Kg.) referable to the initial value. When the changes in body weight are correlated with the fluctuations in exchangeable sodium content, it becomes apparent that in 8 of the 11 subjects (cases 1 to 8), an increase of at least 20 per cent in body weight cannot be accounted for on the basis of alterations in the exchangeable sodium content; the assumption is made in this calculation that the changes in exchangeable sodium content are due solely to those in the extracellular fluid sodium. Of the remaining three subjects, one (case 9) did not develop the typical appearance of hyperadrenalism; one developed the clinical signs while he was losing weight (case 10), and the other showed no significant weight change as the moon facies and buffalo hump appeared.

Changes in Serum Sodium Concentration (table 1). In eight instances the initial serum sodium concentrations, although still within the normal range, was below 140 mEq. per liter. In all of these subjects the serum sodium concentration rose above 145 mEq. per liter while they were being treated with corticotropin. In the remaining three subjects, the initial serum values were between 144 and 148 mEq. per liter. In these individuals, no significant increases were noted during corticotropin therapy.

In some instances (cases 1, 2, 3, 4, 7 and 11) the serum sodium concentration decreased as the dosage of corticotropin was decreased or discontinued.

COMMENT

There are several possible explanations for the fact that the prolonged administration of corticotropin produced increases in body weight which were out of proportion to the changes in exchangeable sodium content: (1) The administration of corticotropin might substantially alter the amount of sodium available for exchange with the radioisotope. (2) The observed changes in weight and Na-e may be due
to a contaminant of the Acthar gel used, such as Pitressin. (3) The initial catabolic effect of corticotropin on protein metabolism may be reversed by prolonged administration, so that body tissue is deposited and body weight increased thereby. (4) There may be an increase in the intracellular water and electrolyte content and osmolality, or both, without an associated increase in the intracellular sodium content. (5) Prolonged therapy with corticotropin may result in an excessive accumulation of body fat. This may be a specific effect on fat metabolism, or it may be a reflection of an increase in appetite and food intake.¹

(1) No data are currently available which suggest that corticotropin may alter the exchangeability of sodium.

(2) Although it has been previously suggested that the gain in weight not explained by changes in nitrogen, sodium or potassium may be a Pitressin effect, the lack of diuresis and weight loss on discontinuation of therapy argues against this possibility. Were this simply a retention of water due to an antidiuretic effect, the serum sodium concentration should have fallen.

(3) Although the administration of corticotropin usually results in negative nitrogen and potassium balance, positive nitrogen balance may occur, provided the dietary intake is great enough, and children and adolescents on Acthar gel do have enormous appetites. Therefore, the discrepancy between the increase in body weight and the changes in exchangeable sodium contents can be attributed to an increase in nonextracellular body tissue. While it is recognized that these changes may in part be the effects of normal body growth, it is difficult to explain all of them solely on this basis. In two subjects (cases 10 and 11) signs of hyperadrenalism appeared at a time when both the body weight and the exchangeable sodium content were decreasing. This observation suggests that the signs of hyperadrenalism may be due to a change in body composition relative to an increase in body fat or intracellular water content, rather than to simply an increase in body muscle mass.

(4) In the calculation of the “unexplained weight change”, the assumption was made that the change in exchangeable sodium content was a reflection of changes in the extracellular sodium content, although it is recognized that the exchangeable sodium includes nonextracellular reservoirs such as muscle cells and bone. Changes in intracellular water and electrolytes, as well as extracellular water, might explain the observed alterations in body weight and exchangeable sodium content. For instance, if there is no change in intracellular osmolality, then an unchanged total exchangeable sodium, which includes intracellular sodium, with an increase in body weight would mean that the increase in intracellular fluid would have been due primarily to an increase in potassium. This certainly would not be in the expected direction in patients receiving corticotropin.

The increase in serum concentration of sodium during corticotropin therapy suggests that a redistribution of water into the intracellular phase may have occurred. Such a change could occur as a result of a large change in osmolality of intracellular solutes or cations. However, the only way in which this intracellular water increase could occur would be by a positive balance of potassium; this would be unlikely during corticotropin therapy. Deane and his co-workers have reported that, in one of two patients with acute rheumatic fever treated with corticotropin, 100 mg. daily for 34 days, the body weight increased progressively from 53.9 to 60.0 Kg. The exchangeable sodium content remained constant, but the total water content increased progressively. These data suggest that the intracellular water content was increased. However, it is difficult to explain increases of 25 to 61 per cent of the body weight, observed in the present series, on this basis alone.

(5) Carcasses of rats treated with corticotropin, when compared with those of controls on the same food intake, have a relative and absolute increase in fat content. The signs of hyperadrenalism produced by the prolonged administration of a relatively large dose of corticotropin resembles those of spontaneous Cushing’s syndrome. In the latter condition, deposits of fat, most conspicuously in the face, the neck and the trunk, have been demonstrated by histologic means. Although no
direct evidences regarding this matter are available from this study, it appears most likely that the observed discrepancy between the changes in body weight and the exchangeable sodium content can be attributed in large measure to an accumulation of body fat.

**Summary**

Serial measurements of the body weight and of the exchangeable sodium content (Na-e) were made in 11 subjects with acute rheumatic fever who were being treated with long-acting corticotropin in daily doses ranging from 2.0 to 5.7 units per Kg.

In all but one subject the typical clinical signs of hyperadrenalism developed. Eight of the 11 subjects showed at least a 20 per cent increase in body weight which was out of proportion to the changes in exchangeable sodium content.

The results suggest that the prolonged therapy of rheumatic fever with adrenocorticotropin results in an alteration in body composition, which is characterized by a relative decrease in body sodium content. It is suggested that the total body fat content may have been increased.

**Acknowledgment**

We wish to express our appreciation to Dr. Robert H. Alway and the other members of the Department of Pediatrics for their cooperation and assistance.

**Summario in Interlingua**

Esseva executate mesuraciones serial del peso corporee e del contento de natrium ex-

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