Effect of Prolonged Steroid Therapy for Rheumatic Fever on the Exchangeable Potassium Content and Body Weight

By Jerry K. Aikawa, M.D.

With the technical assistance of Aaron J. Blumberg

Serial measurements of the body weight and exchangeable potassium content were made in 13 children with acute rheumatic fever who were being treated with large doses of corticotropin or cortisone. In 8 subjects the clinical signs of hyperadrenalism developed. Seven of the 13 subjects showed at least a 20 per cent increase in body weight, which could not be explained on the basis of changes in the body's exchangeable potassium content. This weight gain is thought to be due to an increase in total body fat.

The prolonged administration of cortisone or corticotropin (ACTH) in therapeutic doses produces the physical signs of hyperadrenalism. Previous studies have demonstrated that the increase in body weight resulting from such therapy in rheumatic children cannot be accounted for solely on the basis of retention and redistribution of sodium and water, since the variations in the exchangeable sodium content of the body do not parallel the changes in body weight. The results of these studies suggested that the change in body composition might be due to an increase in fat; however, the possibility of an increase in total muscle mass as a cause of the weight gain could not be completely excluded.

The purpose of the present study on rheumatic children was to investigate further the nature of the alterations in body composition and weight during the prolonged administration of cortisone or long-acting corticotropin (in the form of Acthar gel). Radioactive potassium (K⁴²) was used for this investigation.

Material and Methods

Subjects. Thirteen hospitalized children, 9 boys and 4 girls, with the diagnosis of acute rheumatic fever were studied. Their ages ranged from 5 to 15 years. All 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 cortisone in a daily dosage of 5.5 to 9.4 mg./Kg. of initial body weight. In 10 of the 12 patients treated according to this plan, the initial dosage of cortisone ranged between 6.1 and 7.9 mg./Kg. One patient (case 7, table 1) was treated with corticotropin, starting with a dose of 2.3 units/Kg. These dosages of cortisone or corticotropin were maintained until the clinical and laboratory evidences of rheumatic activity had subsided, at which time they were gradually reduced. If signs of rheumatic activity recurred, the dosage was increased to an intermediate level until all evidences of activity had again subsided. The longest duration of continuous cortisone therapy was 124 days and the shortest, 57 days. Acthar gel was administered for 119 days in case 7.

All patients were placed on a regular hospital diet and received supplemental feedings between meals as desired. All received oral supplements of potassium as chloride or citrate, 2 to 3 Gm. daily.

Isotopes. Isotopic potassium (K⁴²)* was prepared for injection in the manner previously described, in sterile physiologic saline solution.

Determination of Exchangeable Potassium Content (Kₑ). Each subject received an intravenous injection of radioactive potassium (1.5 µc./Kg. of body weight) between 8:30 and 10 a.m. All urine voided thereafter until 6 a.m. the following day was collected, and the Kₑ content of the pooled specimen was determined. Determinations of the specific activity were made on 3 spot samples of urine obtained at 7, 8, and 9 a.m. the day after injection.

The mathematical calculation of the value for the

* Kₑ was supplied by the Oak Ridge National Laboratory, Oak Ridge, Tenn., on allocation from the U. S. Atomic Energy Commission.

From the Department of Medicine, University of Colorado School of Medicine, Denver, Colorado.

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# PROLONGED STEROID THERAPY FOR RHEUMATIC FEVER

| Case | Age (yr.) and sex | Initial weight (Kg.) | Initial dose (mg./day) | Maximum dose (mg./day) | Initial dose (mg./Kg.) | Total dose (Gm.) | Duration of therapy (days) | Signs of hyper-adrenalinism | Days of therapy | Change in wt. (Kg.) | Exchangeable K Ke (mEq.) | Exchangeable K Ke/wt. (mEq./Kg.) | Exchangeable K Ke/K (mEq./Kg.) | Serum concentration Na (mEq./L.) | Serum concentration K (mEq./L.) |
|------|-------------------|----------------------|------------------------|------------------------|------------------------|------------------|--------------------------|----------------------------|----------------|-------------------|--------------------------|--------------------------------|-------------------------------|--------------------------------|--|------------------|
| 1    | 9 M               | 26.4                 | 200                    | 7.6                    | 13.65                  | 110              | +                        |                            | 13             | +0.9              | 1191 43.6               | 1003 36.2                   | 1134 49.2                    | 123 4.6                        | 4.9                        | 5.0                        |
| 2    | 6 M               | 20.6                 | 135                    | 6.6                    | 9.53                   | 83               | +                        |                            | 3              | -0.5              | 780 38.8                | 1103 38.8                   | 1035 46.1                    | 157 4.6                        | 4.5                        | 6.4                        |
| 3    | 11 M              | 27.5                 | 200                    | 7.3                    | 10.08                  | 63               | +                        |                            | 8              | +1.0              | 1314 46.1               | 1260 43.1                   | 1160 48.6                    | 157 4.6                        | 5.6                        | 4.6                        |
| 4    | 15 M              | 68.2                 | 375                    | 5.5                    | 17.85                  | 87               | +                        |                            | 75             | +10.9             | 2873 36.3               | 1361 37.5                   | 1261 41.2                    | 150 4.6                        | 3.9                        | 3.6                        |
| 5    | 10 F              | 31.0                 | 200                    | 6.5                    | 18.63                  | 105              | +                        |                            | 102            | +12.7             | 2284 28.2               | 1395 32.3                   | 1295 36.4                    | 149 4.6                        | 4.7                        | 4.3                        |
| 6    | 5 M               | 15.9                 | 150                    | 9.4                    | 6.43                   | 59               | +                        |                            | 11             | +1.4              | 915 52.9                | 713 37.3                    | 613 32.2                     | 149 4.6                        | 5.2                        | 4.6                        |
| 7    | 14 F              | 43.6                 | 100*                   | 2.3                    | 6359*                  | 119              | +                        |                            | 58             | +7.8              | 2045 39.8               | 728 37.3                    | 628 32.2                     | 151 4.6                        | 4.0                        | 5.0                        |
| 8    | 12 M              | 37.1                 | 250                    | 6.7                    | 11.08                  | 63               | +                        |                            | 41             | +5.5              | 1873 43.9               | 1287 29.4                   | 1187 35.1                    | 148 4.6                        | 4.3                        | 4.3                        |
| 9    | 13 F              | 54.1                 | 350                    | 6.5                    | 21.90                  | 62               | 0                        |                            | 6              | +0.4              | 1598 29.3               | 1600 29.5                   | 1500 35.1                    | 139 4.6                        | 3.8                        | 4.8                        |
| 10   | 8 F               | 19.1                 | 150                    | 7.9                    | 13.28                  | 124              | 0                        |                            | 3              | -2.6              | 614 33.0                | 647 32.4                    | 637 32.1                     | 148 4.9                        | 4.9                        | 5.1                        |
| 11   | 6 M               | 18.0                 | 120                    | 6.7                    | 6.06                   | 58               | 0                        |                            | 20             | +2.1              | 963 47.9                | 954 45.7                    | 944 44.6                     | 150 4.6                        | 4.3                        | 5.7                        |
| 12   | 12 M              | 32.7                 | 200                    | 6.1                    | 9.58                   | 102              | 0                        |                            | 83             | +8.7              | 1214 29.3               | 1787 42.2                   | 1454 49.2                    | 142 4.6                        | 4.3                        | 4.7                        |
| 13   | 8 M               | 27.3                 | 175                    | 6.4                    | 6.50                   | 57               | 0                        |                            | 36             | +4.1              | 1410 44.9               | 1376 43.1                   | 1346 46.4                    | 153 4.6                        | 4.1                        | 4.4                        |

* Dosage of Acthar gel (units).
exchangeable potassium content of the body has been described in detail previously.  

Preliminary studies in this laboratory confirmed the observations of Corsa and his associates that the specific activity of potassium in the urine of both diseased and normal subjects reaches an equilibrium within 18 hours. The mean difference in specific activity among the 3 spot specimens, when expressed as percentage of the mean K, was 4.57 ± 2.76 per cent. In another group of 11 hospitalized subjects who were in a steady state, 2 K, determinations made in this laboratory within a period of 2 weeks agreed within a mean of 2.12 ± 1.10 per cent.

The total number of determinations of exchangeable potassium content was 48; a minimum of 2 and a maximum of 5 serial determinations were performed on each subject, usually at intervals of 2 to 4 weeks. Each patient was observed for a minimum of 65 days.

Measurement of Radioactivity. The radioactivity of the urine 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 physical decay of the isotope. Sodium and potassium concentrations in the serum, and potassium concentration in the urine were determined with a Baird flame photometer, by the lithium internal standard method.

Results

The results are presented in table 1.

Signs of Hyperadrenalism. Eight of the 13 subjects (cases 1 to 8) showed obvious clinical signs of hyperadrenalism—moon face, cervical and supraclavicular fat pads (buffalo hump), and acne—while being treated with cortisone or corticotropin. In the other 5 subjects (cases 9 to 13) some fullness of the face developed but there were no other obvious manifestations. If the length of hospital stay gives any indication, there was no relationship between the development of hyperadrenalism and the therapeutic effectiveness of the drug; in the group of patients with marked hyperadrenalism the mean duration of hospitalization was 104 days (range, 75 to 140), whereas in the group with mild signs the mean duration was 96 days (range, 65 to 124).

Changes in Body Weight. In 12 of the 13 subjects (all except case 9) the body weight increased by at least 10 per cent. In 7 of these patients (cases 1, 2, 3, 5, 6, 7, and 12) the weight gain was more than 20 per cent of the initial value. The greatest increase was observed in a girl (case 5) who showed a steady gain in weight to a maximum of 50 per cent of the initial value on the one hundred and second day of cortisone therapy. In 1 patient treated with corticotropin (case 7) the weight gain was similar to that seen in most of the children given cortisone. One girl (case 9) failed to gain weight, although she showed some fullness of the face.

Although there was considerable variability, the increase in body weight appeared to be progressive and related to the duration of therapy (fig. 1). No definite relationship was observed between the changes in body weight and the therapeutic effectiveness of cortisone or corticotropin. The mean duration of hospitalization in those subjects whose weight

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**Fig. 1.** Weight changes in rheumatic subjects treated with cortisone or corticotropin.

**Table 2.—Summary of Clinical and Laboratory Findings During Steroid Therapy of Acute Rheumatic Fever**

<table>
<thead>
<tr>
<th>Case</th>
<th>Signs of hyperadrenalism</th>
<th>Weight gain &gt;20% initial wt.</th>
<th>Decrease in K&lt;sub&gt;e&lt;/sub&gt;/wt. &gt;5 mEq. Kg.</th>
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* Treated with corticotropin. All other patients treated with cortisone.
gain amounted to more than 20 per cent of the initial body weight was 110 days (range, 75 to 140), whereas the mean duration in those subjects whose weight gain was less than 20 per cent of the initial body weight was 91 days (range, 65 to 124).

Changes in Exchangeable Potassium Content (K_e). With 1 exception (case 12) all initial values for exchangeable potassium content, when related to body weight, were within the range previously established for normal adult men and women.\(^5\) \(^6\) Data of a similar nature for normal children are not yet available.

In the 8 patients who had definite clinical evidences of hyperadrenalism the value for K_e/wt. showed a rather consistent decrease, which was proportional to the duration of therapy with cortisone or corticotropin. In every instance the final value for K_e/wt. was at least 5 mEq./Kg. lower than at least 1 of the previous values obtained in the same patient. Furthermore, the decrease in the value for K_e/wt. was accompanied in every instance by an increase in total body weight. There was, however, no consistent pattern of change in the absolute values for K_e. While 2 subjects (cases 3 and 7) showed no significant change between the initial and final values of K_e, 3 (cases 1, 2, and 5) showed an increase of 15 per cent or more and 3 (cases 4, 6, and 8) showed a decrease of 15 per cent or more.

The 5 patients in whom no overt clinical manifestations of hyperadrenalism developed did not show a definite pattern of change in the values for K_e/wt. In 1 subject (case 9) the K_e was observed for less than 40 days after the initiation of cortisone therapy, and showed no change; this was the only patient whose weight did not increase by more than 10 per cent of the initial value. She was relatively obese prior to therapy and remained so during the period of observation. The other girl in this group (case 10) showed an increase in K_e and K_e/wt. during therapy, the final values on the hundredth day being 29 per cent and 4 mEq./Kg. higher than the respective initial values. In the 3 boys (cases 11, 12, and 13) the values for K_e/wt. were in the range of 42 to 44 mEq./Kg.; except for case 12, serial determinations of the values for K_e and K_e/wt. showed no significant changes.

Changes in Serum Electrolyte Concentration. Except for 1 determination each in cases 1 and 10, all values for serum sodium were within the normal range of 135 to 155 mEq./Kg. All values for serum potassium were within the normal range of 3.5 to 5.5 mEq./Kg.

Discussion

The prolonged administration of large doses of cortisone or corticotropin to rheumatic subjects may produce clinical manifestations of hyperadrenalism, which are usually associated with an increase in body weight. Since it has been previously demonstrated that this weight gain is greater than could be accounted for by changes in the exchangeable sodium content of the body,\(^1\) it is presumed that some explanation other than retention of sodium and water must be sought.

Because corticotropin was used exclusively in the previous study, it was not known whether the changes in weight and exchangeable sodium content were due specifically to the corticotropin or to a contaminant of the Acthar gel, such as pitressin. Since similar changes have been observed in the present study with cortisone, the possibility of a contaminant does not appear likely.

There is the possibility that the initial catabolic effect of corticotropin or cortisone on protein metabolism may be reversed by prolonged administration, so that an increase in muscle mass is responsible for the weight gain. It has been previously demonstrated that positive nitrogen balance may be attained during steroid therapy, provided the dietary intake is great enough.\(^7\) Such an anabolic process should result in an increase in the exchangeable body potassium content, since muscle mass would be increased. It is evident that under the circumstances of the present study the total body content of potassium did not show a consistent increase while a patient is receiving large doses of cortisone or corticotropin. In fact, 3 of the 13 subjects showed a decrease in K_e, and 5 showed no appreciable change. Hence, the anabolic effect per se cannot explain all of the
changes in body weight, nor can they explain the clinical manifestations of hyperadrenalism.

It is highly unlikely that the weight gain is due to an increase in the intracellular content of water and electrolytes, and in osmolarity, or in both, without an associated increase in the intracellular sodium content. Such an intracellular water increase can occur only in the presence of a positive balance of potassium and the data show no consistent trend in this direction.

The data from the present study confirm the clinical impression that prolonged therapy with corticotropin or cortisone may produce an excessive accumulation of body fat. This may result from a specific effect on fat metabolism, or may reflect an increase in appetite and food intake. In favor of the former interpretation is the observation that carcasses of rats treated with corticotropin, when compared with those of controls on the same food intake, show a relative and absolute increase in fat content. On the other hand, children and adolescents on cortisone or corticotropin therapy do have enormous appetites.

The signs of hyperadrenalism produced by the prolonged administration of relatively large doses of cortisone or corticotropin resemble those of spontaneous Cushing's syndrome. In the latter condition, deposits of fat, most conspicuous in the face, neck, and trunk, have been demonstrated by histologic means. Although no direct evidences supporting this hypothesis can be found in this or the previous study, it appears most likely that the changes in body weight and in the exchangeable sodium and potassium contents can be attributed largely to an accumulation of body fat.

**Summary**

Serial measurements of the body weight and exchangeable potassium content (K_e) were made in 13 children with acute rheumatic fever—1 who was being treated with long acting corticotropin and 12 who were being treated with cortisone in daily doses ranging initially from 5.5 to 9.4 mg./Kg. of body weight.

All but 1 subject showed at least a 10 per cent increase in body weight. Eight manifested the typical clinical signs of hyperadrenalism. In all of these 8 subjects the values for K_e/wt. decreased during therapy, suggesting that the increase in body weight was due to a change in body composition. The fact that no consistent change in K_e was observed indicates that the increase in body weight was not due solely to an increase in muscle mass.

The results demonstrated that the change in body composition observed during the prolonged therapy of rheumatic fever with cortisone or corticotropin is characterized by a relative decrease in the potassium as well as the sodium content of the body. It is suggested that the total fat content of the body may have been increased.

**Summario in Interlingua**

Esseva facite mesurationes del peso corporee e del contenue de kalium excambiable (K_e) in 13 juvenes con acute febre rheumatic—1 qui esseva tractate con corticotropina e 12 qui esseva tractate con cortisona in doses diurne (initialmente) inter 5,5 e 9,4 mg per kg de peso corporee.

Omne le subjectos, con un exception, monstrava al minus 10 pro cento de augmento de peso corporee. Octo manifestava le typic signos clinic de hyperadrenalismo. In omne iste 8 subjectos, le proportion K_e/peso descreseva durante le therapia. Isto suggereva que le augmento del peso corporee esseva debite a un alteration in le composition del corpore. Le facto que nulle systematic alteration del K_e esseva observate indica que le augmento del peso corporee non esseva exclusivemente debite a un augmento del massa muscular.

Le resultatos demonsra que le alteration del composition corporee observate durante le prolongate therapia de febre rheumatic con cortisona o corticotropina es caracterisate per un relative reduction del contenue de kalium e etiam de natrium in le corpore. Nos opina que le contenue total de grassia in le corpore esseva possiblemente augmentate.

**References**

PROLONGED STERIOD THERAPY FOR RHEUMATIC FEVER


Analysis of 3,896 patent ductus operations by 49 cooperating surgeons is presented. Of these, 2,929 operations were performed in children and 967 in adults.

The data show a sharp upswing in the 2 most significant preoperative symptoms, myocardial insufficiency and infection, between the children and the adults. The over-all operative mortality was 2.77 per cent (children 2.3 per cent; adults 5.5 per cent). The clinical results in the survivors was considered satisfactory in 98.3 per cent of the children and 95.5 per cent of the adults.

In response to 4 specific questions, the following was ascertained:
1. Surgical Technic. The majority of the investigators favored division of the duct as opposed to ligation. There was no difference in mortality, however, between the 2 series.
2. Pulmonary Hypertension. In regard to ductal interruption in the presence of pulmonary hypertension, opinion was overwhelming that it should be done.
3. Reversal of Shunt. When the shunt has reversed from a predominantly left-to-right flow to a right-to-left one, most surgeons opposed surgery. Some investigators, however, thought that if the pulmonary artery pressure fell after temporary clamping, the duct should be divided.
4. Absence of Cardiac Enlargement and Symptomatology. All but 1 of the surgeons favored ductal interruption in the absence of cardiac enlargement or clinical symptomatology.

Supplementary data, from a more limited group of surgeons, revealed: most previously enlarged hearts decreased to normal size after surgery; 7.1 per cent of cases had a coexistent aneurysm (ductus, pulmonary artery, or aorta); hemorrhage at operation was the largest single cause of death.

The committee concluded that the operation is a standardized and safe procedure, that the finding of a patent ductus, in the absence of a right-to-left shunt, is a definite indication for surgery, and that the operation is optimally performed during childhood.

MAXWELL
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