Pathophysiology of Rheumatic Fever

Alterations in the Na\(^{24}\) Space and in the Exchangeable Sodium and Potassium Contents

By Jerry K. Aikawa, M.D.

Radioisotopic technics were used to explore physiologic aberrations that may characterize individuals with acute rheumatic fever. No significant changes were noted in serial measurements of the blood volume or serum sodium and potassium concentrations. Most of the individuals with severe disease showed an initial value for radiosodium space of more than 330 ml./Kg. of body weight, with no evidence of edema. The exchangeable sodium content of the body correlated well with the radiosodium space. These changes are difficult to explain solely on the basis of extracellular edema, and are interpreted as suggesting that the intracellular content of sodium or that in bone is increased during acute rheumatic fever. An intracellular increase in sodium may be due to an alteration in the permeability of cell membrane induced by an immune mechanism.

At the present time there is much evidence to support the hypothesis that rheumatic fever is a consequence of a hypersensitivity reaction to an antigen or antigens produced by a previous infection with a beta hemolytic streptococcus. Although extensive epidemiologic and bacteriologic studies on the pathogenesis of rheumatic fever have been made, little work has been done on the nature of the abnormal physiologic processes occurring during the acute disease state. Data presented in a previous preliminary note suggested that acute rheumatic fever may be associated with an alteration in the permeability of cell membranes. Such a hypothesis is compatible with the known effects of experimental in vivo antigen-antibody reactions on the distribution of body fluids and electrolytes.

The purpose of the present study was to make further physiologic measurements in rheumatic subjects, following the alterations in the distribution of electrolytes by means of radioactive isotopes of sodium and potassium.

Material and Methods

Subjects. Twenty patients, 14 males and 6 females, with the diagnosis of acute or chronic active rheumatic fever were studied. Their ages ranged from 5 to 41 years, and 16 patients were under 17 years of age. The diagnosis was made on the basis of the history and the physical signs, according to the diagnostic criteria of Jones. The cases were divided into 3 categories according to the clinical severity of the disease, and these groups were further subdivided according to the type of treatment given (table 1). Group 1: Eleven patients had clinical and laboratory evidences of carditis, with persistence of rheumatic activity for longer than a month after the onset of symptoms; these 11 cases were classified as severe (3+). Group 2: Four patients who had evidences of carditis recovered within a month after the onset of the rheumatic process, and their cases were classified as moderately severe (2+). Group 3: Five patients had rheumatic fever with no evidence of carditis, and responded very promptly to hospitalization and therapy; these cases were considered mild (1+).

The general plan of therapy was to administer acetylsalicylic acid, sodium salicylate, aminopyrine, cortisone, or ACTH until the clinical and laboratory evidences of rheumatic activity had subsided. The dosage of the drug was then gradually reduced. If signs of rheumatic activity recurred, an intermediate dosage was continued until all signs of rheumatic activity had again subsided.

All subjects were given a regular hospital diet containing a maximum of 3 to 4 Gm. of sodium daily.

Isotopes. Isotopic sodium (Na\(^{24}\)) and potassium (K\(^{38}\)) were prepared for injection in the manner previously described. Measurement of Radioactivity. Early in the study, the activity of the urine and serum specimens was

* K\(^{38}\) and Na\(^{24}\) were supplied by the Oak Ridge National Laboratory, Oak Ridge, Tennessee, on allocation from the U. S. Atomic Energy Commission.
Table 1.—Classification of Cases

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<tr>
<th>Clinical severity</th>
<th>Therapy</th>
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<td>Salicylates</td>
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<td>ACTH</td>
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<td>3+ (Group 1)</td>
<td>2, 3, 9, 11*</td>
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<tr>
<td>2+ (Group 2)</td>
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<td>1+ (Group 3)</td>
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* The figure indicates the case number in the text, tables, and figure 1.

Radiosodium Space. The volume of dilution of the injected Na\textsuperscript{24} at 3 hours was calculated as follows:

\[
\frac{\text{Na}_{24} \text{ space in liters}}{\text{total Na}_{24} \text{ activity injected} / \text{serum Na}_{24} \text{ concentration per liter at 3 hours}}
\]

The exchangeable potassium content was determined in a manner similar to the determination of the exchangeable sodium content and has been previously described.\textsuperscript{4,5}

Determination of Blood Volume. The plasma volume was determined by the T-1824 dye (Evans blue) method.\textsuperscript{4} The hematocrit value was determined on venous blood collected without stasis in bottles containing potassium and ammonium oxalate; the Wintrobe hematocrit tubes were centrifuged for 30 minutes at 3,000 revolutions per minute. The total blood volume was calculated from the hematocrit reading and the plasma volume.

Results

Radiosodium (Na\textsuperscript{24}) Space

Serial measurements of the radiosodium space were available in 17 patients (table 2, fig. 1). The upper range of normal for this value is considered to be 330 ml./Kg.\textsuperscript{4}

Group 1. Serial Na\textsuperscript{24} space determinations were made in 10 of these cases (fig. 1). In 5 patients (cases 2, 7, 9, 11, and 12) the initial determination was obtained within 10 days after the onset of symptoms; with 1 exception (case 7) all initial values were greater than 330 ml./Kg., the highest value being 528 ml./Kg. (case 6). In the remaining 5 patients (cases 3, 6, 8, 10, and 17) the initial measurement was made between 20 and 62 days of the onset of the disease, and all values were above 330 ml./Kg. Thus, in only 1 instance (case 7) was the initial value for Na\textsuperscript{24} space lower than 330 ml./Kg. None of these 10 individuals had clinically demonstrable edema at any time during the period of observation. In

determined with a dipping Geiger-Müller tube and a scaling circuit. Recent measurements have been made with a well-type scintillation counter. A total of 10,000 counts were made on each sample. All determinations were corrected for physical decay.

Determination of Serum Sodium and Potassium. The sodium and potassium concentrations in the serum or urine were determined early in the course of the study with a Beckman flame photometer by the direct method, and recently with a Baird flame photometer, by the lithium internal standard method.

Procedure

Determination of Exchangeable Sodium Content (Na\textsubscript{e}). Each subject received from a calibrated syringe 1.5 μc. Na\textsuperscript{24} per Kg. of body weight, contained in a sterile 0.9 per cent solution of sodium chloride. All urine voided for the next 24 hours was collected, and the Na\textsuperscript{24} content of the pooled specimen was determined. Blood specimens were obtained at 3 and 24 hours after the injection of Na\textsuperscript{24}, and the specific activity of sodium in the serum was determined. The following formula was used to calculate the value for the exchangeable sodium content of the body:

\[
\text{Na}_{e} = \frac{\text{Na}_{24} - \text{Na}_{23}}{\text{Na}_{24} / \text{Na}_{23}}
\]

\[
\text{Na}_{24} = \text{quantity of exchangeable sodium in milli-equivalents (mEq.).}
\]

\[
\text{Na}_{24} = \text{quantity of radiosodium administered.}
\]

\[
\text{Na}_{24} = \text{quantity of radiosodium excreted in the pooled specimen of urine.}
\]

\[
\text{Na}_{24} = \text{concentration of radiosodium in the serum at 24 hours.}
\]

\[
\text{Na}_{24} = \text{concentration of nonradioactive sodium in the serum at 24 hours.}
\]

\[
\text{Na}_{24} / \text{Na}_{23} = \text{specific activity of the serum at 24 hours.}
\]

Preliminary studies in this laboratory revealed that the Na\textsubscript{e} measurement was reproducible within 5 per cent in edema-free, hospitalized subjects with various chronic diseases whose condition was stabilized.
### Table 2—Changes in the Radiosodium Space, Exchangeable Sodium Content, and Serum Electrolytes During Rheumatic Fever Therapy

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<th>Na(_e) (mEq./Kg.)</th>
<th>Serum electrolytes (mEq./L.)</th>
<th>ESR (mm./hr.)</th>
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<td>49</td>
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<td>4.0</td>
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</table>

ESR = erythrocyte sedimentation rate.
ASA = acetylsalicylic acid or sodium salicylate.

All instances except 2 (cases 7 and 8), subsequent values were at least 50 ml./Kg. lower than the initial values, the maximum decrease being 230 ml./Kg. (case 2).

Eight of the 10 patients in this group gained weight (0.4 to 8.3 Kg.) at a time when the absolute value for the Na\(^{24}\) space was decreasing. Two patients (cases 3 and 8) lost weight. In one (case 3) the Na\(^{24}\) space decreased 11 liters as the body weight decreased 2.3 Kg.; in the other subject (case 8) the Na\(^{24}\) space dropped 2.5 liters as the body weight decreased 2.3 Kg.

Group 2. Initial Na\(^{24}\) space determinations were made between 4 and 11 days of the onset of the disease, and were below 330 ml./Kg. in 2 patients (cases 4 and 5) and above this value in 1 (case 1). In only 1 instance (case 1) did
the Na\textsuperscript{24} space/Kg, subsequently decrease more than 50 ml./Kg. None of the patients had clinical edema.

One subject (case 1) gained 4.8 Kg, and the other 2 (cases 4 and 5) lost 1.3 and 1.4 Kg, in body weight; the Na\textsuperscript{24} space decreased between 2 and 3 L, during this time.

Group 3. Initial Na\textsuperscript{24} space values obtained in 4 patients between 7 and 23 days of onset ranged between 215 and 328 ml./Kg. In none of these patients did subsequent values decrease more than 50 ml./Kg. None of these 5 patients showed clinical edema.

Four of the 5 subjects in this group gained weight (0.9 to 4.8 Kg.) during the period of study, and 1 (case 15) lost 1.2 Kg. No striking changes in the Na\textsuperscript{24} space were noted in any of these subjects.

**Exchangeable Sodium Content (Na\textsubscript{e})**

Serial measurements of the exchangeable sodium content were available in 14 patients (table 2). The upper range of normal for this value is considered to be 46.0 mEq./Kg.\textsuperscript{7}

**Group 1.** Serial Na\textsubscript{e} measurements were available in 8 patients in this category (cases 6–12, and 17). All initial values were higher than 46.0 mEq./Kg. (range, 48.0 to 64.0
mEq./Kg.), even though edema was not clinically evident. In 7 of the 8 patients (exception, case 8) the Nae/Kg. subsequently decreased more than 5 mEq./Kg. (range, -5 to -26 mEq./Kg.). In 4 of the cases, the lowest value obtained remained higher than 46.0 mEq./Kg.

Group 2. Serial Nae values were obtained in cases 4 and 5. In both cases the initial values for Nae/Kg. were 41.0 mEq./Kg. and were not significantly altered during the period of observation.

Group 3. Serial Nae values were obtained in cases 13-16. Two of the 4 initial values were slightly higher than 46.0 mEq./Kg. (47 and 48 mEq./Kg. respectively in cases 15 and 16). In case 16, a decrease of 5 mEq./Kg. subsequently occurred. The other 3 patients showed no significant changes in this value.

There was excellent correlation between the values for the Na\textsuperscript{+} space and the exchangeable sodium content (fig. 2).

Exchangeable Potassium Content (K\textsubscript{e}).

The reported range for K\textsubscript{e} in normal men is 35.6-55.6 mEq./Kg., the mean being 46.3 mEq./Kg. (table 3). For normal women the range in one series\textsuperscript{8} was 25.1-35.0 mEq./Kg., with a mean of 31.5 mEq./Kg.; in another series\textsuperscript{9} it was 28.6-47.2 mEq./Kg., with a mean of 40.7 mEq./Kg. Data of a similar nature for normal children are not yet available.

Group 1. Serial K\textsubscript{e} determinations in a patient (case 19) with severe acute rheumatic fever rose from a low normal of 780 mEq. (39 mEq./Kg.) on the sixth day to 1208 mEq. (43 mEq./Kg.) as the subject gained 8 Kg. in weight while receiving large doses of cortisol. One patient (case 8) with chronic active rheumatic fever, in whom serial Nae, as well as K\textsubscript{e} determinations were performed, showed normal initial K\textsubscript{e} values which first increased approximately 200 mEq., and subsequently decreased to about 200 mEq. below the initial value. In this subject a reciprocal relationship between the Nae and the K\textsubscript{e} was suggested, since the value for Nae/Kg. increased as that for K\textsubscript{e}/wt. decreased, and the sum of the K\textsubscript{e} and the Nae remained fairly constant at all times.

Group 2. K\textsubscript{e} measurements were available in 2 subjects with moderately severe rheumatic

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TABLE 3.—Changes in the Exchangeable Potassium Content and Serum Electrolytes During Rheumatic Fever Therapy

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Severity</th>
<th>Days after onset</th>
<th>Wt. (Kg.)</th>
<th>K\textsubscript{e} (mEq./Kg.)</th>
<th>Serum electrolytes (mEq./L.)</th>
<th>ESR (mm./Hr.)</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>41</td>
<td>M</td>
<td>2+</td>
<td>15</td>
<td>71.1</td>
<td>41</td>
<td>135 5.4 3</td>
<td></td>
<td>ASA, 2.4 Gm. daily, days 7-20</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>21</td>
<td>70.5</td>
<td>36</td>
<td>145 5.8 8</td>
<td></td>
<td>ASA, 2.4 Gm. daily, days 69-77.</td>
</tr>
<tr>
<td>8</td>
<td>13</td>
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<td>3+</td>
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<td>45.5</td>
<td>41</td>
<td>142 4.4 11</td>
<td></td>
<td>Cortisone, 200 mg. daily, days 79-97</td>
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<td></td>
<td></td>
<td>70</td>
<td>44.5</td>
<td>46</td>
<td>139 3.9 39</td>
<td></td>
<td>ASA, 7 Gm. daily, days 11-22;</td>
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<td></td>
<td>76</td>
<td>43.6</td>
<td>38</td>
<td>145 4.4 32</td>
<td></td>
<td>ASA, 5 Gm. daily + cortisone, 300 mg. daily, days 23-40</td>
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<tr>
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<td>2+</td>
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<td>27</td>
<td>139 4.7 31</td>
<td></td>
<td>Cortisone, 135 mg. daily, days 3-60</td>
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<tr>
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<td>150 4.5 34</td>
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<td>Cortisone, 100 mg. daily, days 4-42</td>
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<td>46</td>
<td>149 5.6 8</td>
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ESR = erythrocyte sedimentation rate.
ASA = acetylsalicylic acid or sodium salicylate.
Table 4.—Changes in the Plasma Volume, Hematocrit, and Total Blood Volume during Rheumatic Fever Therapy

<table>
<thead>
<tr>
<th>Case</th>
<th>Days after onset</th>
<th>Wt. (Kg.)</th>
<th>Plasma volume (ml./Kg.)</th>
<th>Hematocrit (vol. %)</th>
<th>Total blood volume (ml./Kg.)</th>
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with salicylates, $K_e$ decreased by 360 mEq., between 15 and 21 days after onset, but remained within the normal range.

**Group 3.** Two $K_e$ determinations were made in 1 patient (case 20) with a mild disease; both values were within the normal range.

**Other Values.** A serum potassium value of less than 3.5 mEq./L. was found in only 1 patient (case 10), who was receiving ACTH gel at the time of this determination (table 4). A potassium value higher than 5.5 mEq./L. was obtained in 3 subjects (cases 4, 8, and 20).

A serum sodium concentration of less than 134 mEq./L. was found in 3 patients (cases 1, 2, and 3), and a value higher than 150 mEq./L. was obtained in 3 patients (cases 5, 10, and 19). There was no correlation between the changes in the serum sodium concentration and the exchangeable sodium content or the radiosodium space.

The plasma volume changes showed no consistent trend during the course of therapy. In 6 of the 7 patients (cases 1–6) in whom serial hematocrit determinations were made early in the course of the disease, the values increased as clinical improvement occurred. In 1 patient (case 7) it decreased before rising. The total blood volume showed no consistent trends during therapy.

**Discussion**

Factors Influencing the Radiosodium Space. The value for the radiosodium space, as determined by the method used, may be influenced by several factors:

**Interstitial Edema.** Previous studies have shown that values for Na space greater than 330 ml./Kg. are usually associated with clinical pitting edema—as, for example, in congestive heart failure. The increased Na space in rheumatic fever cannot be explained on this basis alone, since values in excess of 500 ml./Kg. were found in the absence of any pitting edema. Furthermore, if the increased Na space were due primarily to extracellular fluid retention, loss of this fluid by diuresis should result in a more or less parallel decline in body weight. In most of the rheumatic subjects the body weight increased during therapy as the Na space decreased, and diuresis did not occur. It
is difficult, therefore, to account for the abnormally high values for Na\(^2\) space solely on the basis of interstitial edema.

**Intercellular Cement Substance.** The rate of diffusion of an ion into the extravascular space following intravascular injection may be influenced by the nature and the state of the intercellular cement substance—the hyaluronic acid and chondroitin sulfuric acid systems. The radiosodium space is increased, for instance, in myxedema, where the excess of colloidal substances in the interstitium causes abnormal retention of salt and water. Such an abnormal physiologic process is manifested clinically by puffiness and generalized nonpitting edema, and thyroid therapy results in loss of body weight and a parallel decrease in the radiosodium space.\(^9\)

The apparent increase in the 3-hour value for the Na\(^2\) space in rheumatic subjects may be explained by an increase in the rate of exchange between the injected radioactive atoms and the native ions in the intercellular cement system. That connective tissue changes occur in acute rheumatic fever has been established. Were this the only factor responsible for the apparent increase in Na\(^2\) space, however, the 24-hour value for exchangeable sodium content would not necessarily be elevated. The finding in the present study of a remarkable correlation between the Na\(^2\) space and the exchangeable sodium content suggests that the body’s store of sodium is indeed increased during acute rheumatic processes; this excess sodium, however, does not appear to be extracellular in an amount sufficient to induce clinical pitting edema.

**Bone Sodium.** If the excess exchangeable sodium is not extracellular, there is a possibility that it might be adsorbed on bone in excessive amounts or exchanged with bone sodium at an increased rate. The nature and regulation of bone sodium are poorly understood, and it is conceivable that an increase in the exchangeable sodium content or the radiosodium space might be due to an abnormality in exchange or storage in bone. However, such a possibility is not thought to be as likely as the following explanation.

**Tissue Cell Membrane.** The data best fit the hypothesis that, in acute or chronic active rheumatic fever, the normal relative impermeability of the tissue cell membrane to the sodium ion is altered, with a resultant increase in the rate of exchange of sodium between the extracellular and intracellular compartments and in the amount of sodium within cells. Thus, the radiosodium space and the exchangeable sodium content are increased to an extent which is out of proportion to the amount of clinical edema present.

This increase in the intracellular store of sodium appears to be accompanied by a decrease in the intracellular content of potassium. While the data on the exchangeable potassium are meager, they suggest that the exchangeable potassium content is lowest early in the course of severe or moderately severe rheumatic fever, when the exchangeable sodium content is highest. This change in equilibrium between the intracellular and extracellular compartments does not appear to be reflected by any consistent alterations in the serum concentrations of sodium and potassium.

An increase in capillary permeability usually results in extracellular edema formation; since edema was not evident in the present study, it is concluded that capillary permeability was not significantly altered. Furthermore, no significant changes were noted in the plasma volume or total blood volume. These data suggest that the greatest physiologic abnormality occurred at the level of the cell membrane and that changes in capillary permeability were slight.

**Relationship to Immune Mechanism.** Recent studies with isotopes have dispelled the previously accepted view that all of the body’s store of sodium and chloride is located extracellularly. It is now recognized that a much more complex situation prevails. The concept of cell membranes impermeable to ions has been supplanted by the view that ionic exchange occurs continuously across a membrane that may actively participate in the process by means of its own enzymes and metabolic processes. It is now believed that concentration gradients are maintained by enzymatically controlled intracellular metabolic processes as well as by physicochemical processes. Inorganic ions are known to play a dynamic role as essential components of enzyme systems. The results of the present study suggest that rheumatic fever...
produces some alterations in such a dynamic process.

It is apparent that any severe disease process, whether produced by a physical, chemical, or biologic agent, will result in abnormal physiologic changes in the body cells. For instance, an increase in the intracellular content of sodium has been reported in such diverse disease states as infant diarrhea, dietary deficiency of potassium, simian malaria, Rocky Mountain spotted fever, serum sickness, congestive heart failure, and experimental burns and trauma. Thus, an increase in the intracellular content of sodium may be a nonspecific response to injury of any type.

The purpose of the present discussion is not to describe in detail the mechanisms involved in these various types of cell injury, but simply to determine whether the physiologic changes observed in acute rheumatic fever can be satisfactorily explained by the hypothesis that rheumatic fever is a hypersensitivity reaction to streptococcal infection. It was formerly assumed that antigenic substances that were injected parenterally remained in the extracellular fluid compartment. Recent studies with tagged antigens, however, have shown that antigenic substances rapidly cross the cell membrane and localize in the mitochondria. It has been suggested that the mitochondria are the anatomic site of protein synthesis, and that antibody production is a modified form of gamma globulin synthesis. An in vivo intracellular union of antigen and antibody might be expected to produce disturbances in the orderly function of intracellular enzyme systems and alterations in membrane permeability.

In the present study, the evidence of an alteration in cell membrane permeability, without evidence of abnormal capillary permeability, suggests that the changes may be due to the tuberculin or delayed type of hypersensitivity reaction, since an increase in capillary permeability is usually evident in an in vivo anaphylactic type of reaction.

Adrenal cortical hormones, under certain conditions, can suppress antibody formation. Although the exact mechanism of this suppression is not known, it has been stated that these substances tend to restore the integrity of cell membranes. The mechanism of action by which salicylates and aminopyrine suppress the rheumatic symptoms and signs is also unknown, but their effect appears to be more than antipyretic. The increased radiosodium space, for instance, persisted for several weeks after initiation of therapy, whereas the fever usually subsided within 48 hours. It has been suggested that both salicylates and aminopyrine stimulate the adrenal cortical secretion. Whatever the exact mechanism of action may be, the data suggest that the abnormal permeability of cell membranes in acute rheumatic fever can be suppressed by all of the therapeutic agents used.

It is obvious that further and more extensive studies of the type reported here are necessary for a better understanding of the patho-immunophysiology of rheumatic fever.

**Summary**

Serial measurements of the radiosodium space and the exchangeable sodium and potassium contents were made in 20 patients with acute or chronic active rheumatic fever, during hospitalization and therapy. Ten of 11 patients with severe disease had an initial value for Na space of more than 330 ml./Kg. of body weight, with no evidence of edema. Most of the subsequent values were lower, at a time when body weight had increased. Such changes were noted infrequently in individuals with mild or moderately severe disease.

The exchangeable sodium content of the body correlated well with the radiosodium space. The exchangeable potassium content of the body tended to be low when the exchangeable sodium content was high. No striking changes were noted in the serum sodium and potassium concentrations.

The results have been interpreted as suggesting that the intracellular content of sodium is increased during acute rheumatic fever, although the possibility of an increase in bone sodium has not been excluded, and that this abnormality may be due to an alteration in the permeability of cell membranes induced by an immune mechanism.

**Summario in Interlingua**

Mesurationes serial del spatio de natrium radioactive e del contento de excambiabile
natrium e kalium esseva facete in 20 pacientes con acute o chronic febre rheumatic. Omnes esseva hospitalisate e sub tractamento. Dece del 11 patientes con grados sever del morbo fabeva un valor initial pro le spatio de Na\textsuperscript{+} de plus que 330 ml per kg de peso corporee. Iste patientes fabeva nulle signo de edema. Le majoritate de lor valores subsequente esseva plus basse, e isto a un tempore quando le peso corporee fabeva accrescite. Tal alteraciones esseva notate infrequentemente in individuos con leve o moderamente sever grados del morbo.

Le contenuto de excambiabile natrium in le corpore esseva ben correlationate con le spatio de natrium radioactive. Le contenuto de excambiabile kalium in le corpore monstrava le tendentia de esser basse quando le contenuto de excambiabile natrium esseva alte. Nulle frappante alteraciones esseva notate in le concentrationes serial de natrium e kalium.

Le resultatos pare indicar che le contenuto intracellulare de natrium es augmentate durante acute febre rheumatic, sed le possibilitate non poti esser neglige che il occurre un augmento del contenuto de natrium in le ossos e que iste anormalitate resulta de un alteration del permeabilitate del membranas celular como effecto de un mecanismo immunologico.

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JERRY K. AIKAWA

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