Treatment of the Low-Salt Syndrome in Congestive Heart Failure by the Controlled Use of Mercurial Diuretics

By Albert L. Rubin, M.D., and Warren S. Braveman, M.D.

The production of the low-salt syndrome in cardiac patients with refractory congestive heart failure is generally attributed either to fluid retention with electrolyte dilution or to excessive salt loss, induced by the frequent administration of mercurial diuretics. The former is often the important etiologic factor. In a study of a group of 25 refractory cardiac patients with normal plasma electrolyte patterns, a hyperchloremic acidosis was produced to restore a responsiveness to mercurial diuretics. During the mercurial-induced diuresis that followed, the urinary sodium concentration was significantly lower than the plasma sodium concentration in all instances. From these observations, a method of treatment of the low-salt syndrome, utilizing mercurial diuretics seemed feasible. This regimen was successfully carried out in two hyponatremic patients with return of plasma sodium to normal and striking clinical improvement.

In cardiac patients with fluid retention, two types of electrolyte imbalance have been associated with a transient refractoriness to mercurial diuretics. One of these is hypochloremic alkalosis, and the other is hyponatremia in association with hypochloremia, the "low-salt syndrome."

The former is a well-defined clinical entity that sometimes occurs in the course of vigorous treatment of the edematous cardiac patient with salt restriction and protracted daily injections of a mercurial diuretic agent. Hypochloremic alkalosis may occur prior to the attainment of optimal body weight. Responsiveness to mercurial diuretics is restored in this situation when the hypochloremia is corrected by the administration of ammonium chloride.

The latter electrolyte imbalance, the "low-salt syndrome," can be present in a number of disease states. These have been discussed recently by Danowski and his associates who call them the "low-salt syndromes" and classify them according to total stores of extracellular sodium—decreased, intact, and increased. The patients discussed in this article would fall into that group demonstrating the "low-salt syndrome" with increased sodium stores and congestive heart failure.

The "low-salt syndrome," as originally described by Schroeder consisted of (1) drowsiness, weakness, and lethargy, (2) loss of appetite, (3) nausea and vomiting and occasionally abdominal or muscular cramps. These symptoms occurred in a setting of (1) a successive depression of urinary volume, (2) decreased urinary excretion of chloride ion, not increasing after mercurial diuretic administration, (3) progressive gain in body weight, (4) rising nonprotein nitrogen content of the blood, and (5) hyponatremia and hypochloremia. The author reported two mechanisms by which this syndrome could be produced: by retention of water and dilution of electrolytes, and by excessive depletion of the body salt, usually associated with the use of mercurial diuretics. The former mechanism is well recognized, having been seen many times in postoperative surgical patients given parenteral glucose in water, and its significance as an etiologic factor in the production
of the "low-salt syndrome" has received recognition.5,6

With regard to the latter mechanism, the question may be raised whether the data establish that mercurial diuretics contribute to the development of the clinical state described. In the original paper on the "low-salt syndrome," only urinary chloride ion concentration was measured. Sodium excretion was not determined. Measuring urinary chloride concentration alone gives a false conception of sodium losses. A greater proportion of the chloride ion than of the sodium ion in the extracellular fluid is excreted in the urine after the administration of mercurials, apparently because such agents act primarily on the chloride ion.7 All the subjects showed significantly positive daily water balance, and, in all cases but one, mercurial diuretics were administered very infrequently and intermittently. Only one of the cases reported showed a significant diuresis as judged by weight loss, after the administration of hypertonic saline solution to correct the electrolyte imbalance. Many did not lose as much weight after therapy as they had gained during their period of oliguria. For these reasons all the cases could represent examples of extracellular fluid expansion with electrolyte dilution, and no direct evidence is presented to incriminate mercurial diuretics as etiologic agents. To state unequivocally that hyponatremia results from the administration of mercurial diuretics, it should be necessary to show that urinary sodium concentrations in the diuresis following drug administration exceeds the plasma concentration of sodium, in a setting where the fluid intake is restricted to approximate the patient's insensible loss (e.g., 1 kilogram of weight loss is equivalent to 1 L. of urine output). To our knowledge, this has never been demonstrated.

In our experience, most patients with refractory edema due to heart failure have normal plasma electrolyte concentrations.8 At this stage in the natural history of their heart disease, these patients are unable to handle water as well as salt. This is not generally appreciated, and while salt intake is rigidly restricted, fluid intake is not. The result is fluid retention, further expansion of extracellular fluid volume, and consequently electrolyte dilution.

Overhydration with resultant expansion of the extracellular fluid volume and dilution of electrolytes would appear to be the most important etiologic factor in the production of this syndrome, which might better be termed the "dilution syndrome."

In 25 refractory cardiac patients with normal plasma sodium and chloride concentrations in whom a hyperchloremic acidosis was produced by means of Diamox (acetazokamide) and ammonium chloride,8 a responsiveness to mercurial diuretics was restored. In all these patients the urinary sodium concentration during the mercurial-induced diuresis was

<table>
<thead>
<tr>
<th>Pt.</th>
<th>Plasma Na⁺ (mEq L⁻¹)</th>
<th>Urine Na⁺ (mEq L⁻¹)</th>
<th>Plasma Cl⁻ (mEq L⁻¹)</th>
<th>Urine Cl⁻ (mEq L⁻¹)</th>
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<tr>
<td>B. E.</td>
<td>137</td>
<td>113</td>
<td>129</td>
<td>132</td>
<td>6.0</td>
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significantly lower than the plasma sodium concentration. Table 1 lists the plasma and urine sodium and chloride concentration and the weight loss in pounds that occurred in a 24 hour period after the administration of 2 ml. of Mercuhydrin (meralluride) in the setting of a hyperchloremic acidosis, on 40 separate patient days. Note that the urine is always hypotonic for sodium with respect to the plasma, and that the concentration of chloride in the urine markedly exceeds that of sodium.

In these patients, plasma sodium concentration remained within normal limits, probably reflecting ion shifts between intracellular and extracellular fluid compartments. In patients with hyponatremia, it was theorized that in a similar situation, plasma sodium concentration might rise toward normal, if homeostatic mechanisms tending to regulate body sodium were functioning. For, if 1 L. of edema fluid is removed from the body with a sodium concentration less than that in the plasma, and is not replaced by fluid administration (i.e., the patient loses 1 Kg. in weight), extracellular fluid sodium concentration should rise.

It appeared to us, developing the premise that this syndrome represented a primary dilution phenomenon, that the aim in therapy should be the mobilization of excess fluid in the expanded extracellular fluid space, rather than elevation of the extracellular fluid sodium content. Accordingly, a group of five patients with heart disease, congestive failure, and refractory fluid retention, who showed azotemia, oliguria, anorexia, and nausea, and who had a marked hyponatremia and hypochloremia were treated with a regimen that had been successful in restoring responsiveness to mercurial diuretics in cardiac patients with refractory fluid retention who had normal plasma electrolyte patterns. This regimen, which utilizes Diamox and aqueous ammonium chloride, has previously been described in detail. No attempt was made to alter plasma sodium concentrations. In the setting of a hyponatremia, an elevated plasma chloride concentration, lowered blood pH, and lowered carbon dioxide combining power, the daily administration of Mercuhydrin resulted in a marked and sustained diuresis in all five cases, during the course of which plasma sodium concentration returned to normal.

Two cases from this group have been selected for this report on the basis of the completeness of their data.

Methods

1. Each patient selected was carefully evaluated to insure adequate digitalization and to rule out complicating disease, such as thyrotoxicosis, infection, or pulmonary infarction.

2. Fluid intake was restricted to less than 1500 ml., and salt intake to 2 grams or less daily.

3. Plasma pH, carbon dioxide combining power, chloride, sodium and potassium, urine output, and urine sodium, potassium, and chloride concentrations were determined daily.

4. Aqueous ammonium chloride was given daily in 5 divided doses of 2 grams each, and Diamox in a single daily dose of 750 mg. by mouth. If the patient's initial carbon dioxide combining power was elevated (as in case 2), Diamox was given without ammonium chloride until its diuretic effect had waned, and then ammonium chloride was added.

5. When the chloride concentration in the urine had risen over 40 millequivalents per liter, Diamox was discontinued and 2.0 ml. of Mercuhydrin were given intramuscularly daily. Ammonium chloride administration was continued throughout the period during which Mercuhydrin was given.

6. Laboratory methods used for determinations of plasma pH and carbon dioxide combining power, plasma and urinary sodium, potassium, and chloride have been previously described.

Case Reports

Case 1. S. S., a 51-year-old white luncheonette owner, was admitted to the New York Hospital for the fifth time in severe congestive heart failure. He had first been hospitalized 2 years before with a myocardial infarction. Subsequent admissions were for control of cardiac decompensation which had its onset 6 months after the occurrence of the myocardial infarction. He was maintained on digitals, a salt-poor diet, and restricted activity.

For 3 weeks prior to his present admission, his dyspnea and orthopnea had become progressively more severe, despite continued use of digitals, frequent mercurial injections, ammonium chloride, bed rest, and salt restriction.

Physical examination on admission revealed a lethargic, severely dyspneic and orthopneic, cyanotic, acutely ill man with a blood pressure of 180/100, pulse 100 (regular), respiratory rate 30 per minute, temperature 39.2 °C. He showed distention of the neck veins, bilateral pleural effusion, rales in both lung fields, cardiomegaly with a gallop rhythm, hepatomegaly, and 4 plus pitting ankle and sacral
edema. Initial laboratory findings included 2 plus albuminuria, hematocrit value 55 per cent, venous pressure (antecubital vein) 300 millimeters of saline, circulation time (decholin, arm to tongue) 40 seconds, blood urea nitrogen 41 mg. per cent, sodium 131 mEq., chloride 98 mEq., and carbon dioxide 25 mEq. per liter.

The patient was initially treated with complete bed rest, 1 Gm. salt diet, oxygen, phlebotomy, and was given additional digitalis until minor toxic symptoms appeared. Despite these measures, he showed no improvement. Table 2 is a tabulation of the daily weight, intake and output, plasma and urine electrolyte concentration, and medications given in this case. After 10 days his weight had risen, and his urine output had fallen below 1000 ml. per day. The blood urea nitrogen was 67 mg. per cent. The plasma sodium had fallen to 122 mEq. and the plasma chloride to 87 mEq. per liter.

During the next 2 weeks, 5 per cent hypertonic saline was administered intravenously in amounts of 100 to 200 ml. on 6 different occasions in an attempt to correct the hyponatremia and hypochloremia. At the end of this period the patient had gained 13 pounds, showed anasarca, and was symptomatically worse. Plasma sodium concentration was 112 mEq. and plasma chloride concentration was 98 mEq. per liter.

At this time, a review of the patient’s clinical course showed that in this 20-day period, a significantly positive daily water balance was present. Fluid intake had averaged 2300 ml. daily, while his urine output averaged 800 ml. daily. During this period, the patient had been afebrile and had not perspired excessively. The major factor in his hypona- tremia and hypochloremia was felt to be dilution, and it was decided that therapy should be directed primarily toward mobilization of this excess total body water.

Accordingly, the patient was given 750 mg. of Diamox in a single dose by mouth and 10 Gm. of aqueous ammonium chloride in 5 divided doses daily for 4 days. Fluid intake was restricted to approximate his urine output plus estimated insensible loss. During this 4-day period of Diamox and ammonium chloride administration, his weight did not change. A hyperchloremic acidosis was produced. The plasma pH fell from 7.43 to 7.27 and plasma chloride rose from 94 to 114 mEq. per liter. Carbon dioxide combining power fell from 22.6 to 8.4 mEq. per liter. No symptoms of acidosis developed. Plasma sodium remained low at 120 mEq. per liter, and plasma potassium stayed within normal limits. Urine output averaged 850 ml. daily with very low-sodium content. Urine chloride content, initially low, rose as the plasma chloride level increased (table 2 and fig. 1).

In this setting of a hyponatremia and hyperchloremic acidosis, Mercuhydrin (2 ml. intramuscularly) was administered daily for 5 days. Ammonium chloride administration was continued, and potassium chloride was given on the second and third days. A striking diuretic response was achieved, with a peak urine output of 815 liters occurring on
the second day of mercurial administration. In this 3-day period, the patient lost 42 pounds in weight. Total daily urinary excretion of sodium and chloride was high, with chloride content exceeding sodium on each day. However, it is most significant to note that with respect to the plasma, the urine each day was hyponatmic so far as sodium was concerned. In this 3-day period, the hyponatremia was corrected, the plasma sodium rising from 120 to 132 mEq. per liter. The patient's electrolyte pattern at the end of this time had returned almost to normal (sodium 132 mEq., potassium 3.4 mEq., chloride 102 mEq., carbon dioxide 28 mM per liter). The blood urea nitrogen had fallen to 18 mg. per cent. Clinically he was dramatically improved and subsequently he could be allowed out of bed. Figure 1 is a graphic representation of the patient's response to this regimen.

This improvement continued in the next 2 weeks with a further 6-pound weight loss on mercurehydrin alone.

In his sixth hospital week, while arrangements for further care at home were being made, the patient died quietly while asleep, apparently from a myocardial infarction or pulmonary embolism.

Case 2. L. T., a 53-year-old white male clerk was admitted to the New York Hospital in pulmonary edema. He had a 20-year history of hypertension and chronic lung disease. When admitted to a hospital 1 year before, he was in chronic heart failure and responded well to a regimen of digitalis, salt restriction, and mercurial diuretics. At that time the laboratory findings included a hematocrit value of 37, a blood urea nitrogen of 15 mg. per cent, and carbon dioxide combining power of 36 mM per liter. The electrocardiogram showed a pattern of left ventricular hypertrophy. Roentgenogram of the chest was compatible with pulmonary emphysema. Gastrointestinal and hematologic work-up revealed no explanation for the low hematocrit value. The patient did well on an ambulatory regimen of digitals, mercurials, and a salt-poor diet until 2 months prior to his present admission, at which time he had an upper respiratory infection, and dyspnea and ankle edema recurred. During the 2 weeks prior to admission, shortness of breath and ankle swelling

FIG. 1. Case 1. A graphic representation of the course of observation. On the ordinates are listed the body weight, plasma electrolyte concentrations and pH, and urine electrolyte excretions and output for each 24-hour period. On the abscissas are listed the medications given and the number of days each medication, or combination of medications, was given.
increased despite mercurial injections twice a week. During this period his fluid intake was high and salt intake was drastically curtailed.

Physical examination on admission revealed a blood pressure of 180/110, pulse 100 (regular), rate 30 per minute, temperature 37.2 C. He seemed both acutely and chronically ill, and was disoriented, dyspneic, and cyanotic. There was grade III retinopathy. Neck veins were distended. The chest had an increased anteroposterior diameter, was hyperresonant to percussion, had diminished tactile fremitus, and fine, medium, and coarse rales throughout. His heart was enlarged to the anterior axillary line, and an apical systolic murmur was present. The liver was felt 5 fingerbreadths below the right costal margin. Ascites and 4 plus ankle and sacral edema were present.

Laboratory findings on admission included urine specific gravity of 1.012 with 2 plus albuminuria, a hematocrit value of 37 per cent, and a blood urea nitrogen of 29 mg. per cent. The venous pressure was 200 mm. of saline in the antecubital vein, and the circulation time was 18 seconds (arm to tongue, decholin). Plasma sodium concentration was 120 mEq per liter. Roentgenogram of the chest revealed cardiomegaly and was compatible with pulmonary emphysema. The electrocardiogram showed a pattern suggestive of left ventricular hypertrophy in the precordial leads, with no axis deviation and clockwise rotation.

With the history of salt restriction, oliguria, weight gain, and high fluid intake, it was felt that the hyponatremia was the result of dilution rather than inordinate urinary losses of salt. Table 3 lists the daily weight, intake and output, plasma and urine electrolyte concentrations, and medications given in this case.

The patient was placed on bronchodilators, bed

<table>
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<tr>
<th>Day</th>
<th>Medication</th>
<th>Blood Urea Nitrogen, mEq/L</th>
<th>Wt. Changes, lbs.</th>
<th>Plasma</th>
<th>Urine</th>
<th>Intake cc./24 hr.</th>
<th>Output cc./24 hr.</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Na⁺ mEq/L</td>
<td>Cl⁻ mEq/L</td>
<td>CO₂ mEq/L</td>
<td>K⁺ mEq/L</td>
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Table 3.—Medications, Daily Weight Change, Plasma and Urine Electrolyte Concentrations, and Fluid Intake and Output in Case 2
rest, salt restriction, and was given a mercurial diuretic the first day. He lost no weight during the first 24 hours, although his pulmonary status improved. He was then given 750 mg. of Diamox by mouth daily for 7 days with 5 Gm. of potassium chloride on the fifth and sixth days. During this time, due to a misunderstanding, fluid intake was not restricted. The patient responded with a diuresis, losing 7.2 Kg. in weight. The major weight loss, 6 Kg., occurred in the first 4 days, during which time the plasma carbon dioxide combining power fell from 37 to 29.5 mM per liter. This initial response to Diamox alone is attributable to the high plasma bicarbonate content. During this period of diuresis the urine contained very little chloride, sodium content was low, and potassium high. At the end of this 6-day period, the plasma sodium was 125 mEq., chloride 93.8 mEq., carbon dioxide combining power 29.5 mM, and potassium 3.4 mEq. per liter. The plasma pH was 7.35, falling from pre-treatment level of 7.47 (fig. 2).

For the next 4 days Diamox and potassium chloride were continued, and 8 grams of aqueous ammonium chloride in 4 divided daily doses were added. During this period the plasma sodium remained at 125 mEq., and the carbon dioxide combining power fell to 21.3 mM per liter. The plasma pH was 7.34 at the end of this period. No significant weight change occurred. Through error, fluid restriction had not yet been instituted. Urinary output averaged 1800 ml. daily.

Urinary chloride excretion, initially low, increased 11 fold in daily stepwise fashion as the plasma chloride concentration returned to a normal level. In this setting of hyponatremia and a normal plasma chloride concentration, Diamox administration was stopped, fluid intake was restricted to 1500 ml. a day and Mercuhydrin, 2.0 ml intramuscularly, was administered daily for 7 days. Ammonium chloride and potassium chloride supplements were continued throughout this period. A sustained diuresis ensued and the patient lost 25.5 pounds in weight. During this period the urine contained a high concentration of chloride ion and a moderately high concentration of sodium ion (table 3). However, each liter of urine was significantly hypotonic for sodium with respect to

\[ \text{WEIGHT} \\
\text{Lbs.} \quad 158 \\
\quad 138 \\
\quad 118 \\
\text{PLASMA} \\
\text{Chloride mEq/L} \quad 102 \\
\quad 82 \\
\text{CO}_2 \text{ mEq/L} \quad 30 \\
\quad 20 \\
\text{pH} \quad 7.40 \\
\quad 7.30 \\
\text{Sodium mEq/L} \quad 130 \\
\quad 120 \\
\text{Potassium mEq/L} \quad 5 \\
\quad 3 \\
\text{URINE} \\
\text{Electrolyte Excretion mEq/24 hr.} \\
\text{Diamox} \quad 500 \\
\text{Diamox + KCl} \quad 1000 \\
\text{Diamox, NH}_4\text{Cl, KCl} \quad 1500 \\
\text{Merc, NH}_4\text{Cl, KCl} \quad 2000 \\
\text{Merc, NH}_4\text{Cl, KCl} \quad 2500 \\
\text{H}_2\text{O} \quad 3000 \\
\text{MEDICATION} \\
\text{DAYS OF ADMINISTRATION} \\
\text{3} \\
\text{2} \\
\text{4} \\
\text{1} \\
\text{1} \\
\text{2} \\

\text{FIG. 2. Case 2. A graphic representation of the course of observation during which the regimen described in the text was used. Where the days of drug administration are more than one, the urine electrolyte excretions and urine outputs graphed represent averages of the number of days recorded in each instance.}
the plasma. Thus, at the end of this mercurial diuretic period, the plasma sodium concentration had risen from 125 to 138 mEq. per liter. Figure 2 is a graphic representation of the patient's response to this regimen.

The patient was symptomatically strikingly improved, was edema free, and had a normal plasma electrolyte pattern. He was discharged from the hospital, and is at present being maintained edema-free on a regimen of salt and fluid restriction, daily ammonium chloride and bi-weekly mercurial injections.

The other 3 patients treated by this regimen showed similar clinical improvement, and rises in plasma sodium concentrations from 118–135 mEq., 119–128 mEq. and 122–136 mEq. per liter, respectively. These changes occurred in the course of a sustained diuresis resulting in each instance in a marked weight loss (14, 16, and 24 pounds respectively).

**Discussion**

The 2 cases reported above typify the group of cardiac patients that we have seen with fluid retention, hyponatremia, and hypochloremia. The positive water balance that we have found to be a consistent feature in these cases is clearly demonstrated. Treatment in this situation poses a difficult problem. In most instances, as in case 1, the administration of hypertonic saline solution in an attempt to correct the hyponatremia does not improve the clinical status of these patients. It often results in a further weight gain and a progression of already distressing symptoms.

A responsiveness to mercurial diuretics was restored by using Diamox and ammonium chloride to produce that rise in plasma chloride concentration necessary to provide for the presentation of an adequate chloride load to the renal tubules. Our empiric observation has been that this state is achieved when the urinary chloride concentration has risen to over 40 mEq. per liter. The mechanism of the action of Diamox in producing a rise in plasma chloride concentration has been studied.9

The significant characteristic of the mercurial-induced diuresis that occurred, once the necessary hyperchloremia has been achieved, was that each liter of urine had a considerably lower sodium content than the extracellular fluid. As a result, with fluid intake restricted, the sodium concentration of the extracellular

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**Fig. 3.** Diagrammatic representation of the changes in extracellular fluid volume and sodium concentration that occur as a result of the diuresis achieved in the setting of a hyperchloremic acidosis by the application of the regimen described in the text.

Sodium 'gain' by body as a result of diuresis of a urine that is hypotonic for sodium with respect to the E.C.F. can be calculated as: $[(120 \text{ (E.C.F. conc./L.)} - 90 \text{ (urine conc./L.)}) \times 7 \text{ (liters of urine)} = 210 \text{ mEq. of sodium available for redistribution in the E.C.F. remaining after diuresis.}$
fluid rose toward normal (fig. 3). Striking clinical improvement occurred in association with the diuresis and the return to normal of the plasma sodium concentration.

Producing an acidosis in an already azotemic patient is potentially hazardous, and the necessity for continued close clinical and laboratory observations cannot be overemphasized. However, with such observations, the acidosis has been without ill effect. The degree of acidosis and rise in plasma chloride concentration necessary to restore a responsiveness to mercurial diuretics varies with each individual patient. The essential indication that the necessary acidic state has been achieved is a rise in urinary chloride concentration. It is to be emphasized that this is unrelated to a specific level of plasma pH or plasma chloride concentration. This principle is clearly demonstrated in the 2 cases reported above. In case 1, the urinary chloride concentration, initially 12.8 mEq per liter, rose to 43 mEq per liter when the plasma pH was 7.27 and the plasma chloride concentration was 114 mEq per liter. By contrast, in case 2 the urine chloride concentration initially 2.8 mEq per liter rose to 78.4 mEq per liter (indicative of an adequate setting for mercurial administration) when the plasma pH was 7.34 and the plasma chloride concentration was only 102 mEq per liter.

The effectiveness of this therapeutic approach, directed primarily toward reducing the expanded extracellular fluid volume, and not primarily toward increasing the sodium content of the extracellular fluid, supports the postulation that the mechanism for development of this syndrome is primarily fluid retention with extracellular fluid expansion, and not salt depletion. In keeping with this view is the role that mercurial diuretics play in the success of this regimen, when heretofore they have been purported to be a significant causative factor in producing the "low-salt" syndrome.

Conclusions

1. An effective regimen for treatment of the "low-salt syndrome" utilizing Diamox, ammonium chloride, and mercurial diuretics has been presented.

2. It is suggested that extracellular fluid expansion with electrolyte dilution is the major factor in the production of the "low-salt syndrome," which might more aptly be termed the "dilution syndrome."

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Summario in Interlingua

1. Es presentate un efficace regime pro le tractamento del "syndrome de basse nivellos de sal," utilizzante Diamox, chlorido de ammonium, e diureticos mercurial.

2. Nós opinas que le expansion extracellular de fluido occurrente in le presentia de dilution electrolytique es le major factor in le production del "syndrome a basse nivellos de sal." Il essera plus appropriate designar iste syndrome como "syndrome de dilution."

References

Treatment of the Low-Salt Syndrome in Congestive Heart Failure by the Controlled Use of Mercurial Diuretics

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