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Low salt syndrome

Robert M. Sorenson
University of Nebraska Medical Center

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Robert M. Sorensen

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When the intake of water is rapidly increased, and urinary volume does not increase proportionately, dilution of electrolytes in extracellular fluids occurs. Beside gain in weight there is oliguria and retention of nitrogen in the blood with the patient complaining of weakness, drowsiness and muscular cramps and becoming prostrated. It was formerly believed that this sequence of events represented "water intoxication" resulting from a high intake of water and low intake of salt.

Further experience with this condition has since accumulated. It is precipitated not only by the excessive intake of water, but commonly by the overenthusiastic use of mercurial diuretics in conjunction with diets low in sodium chloride. It has developed spontaneously when arterial hypertension was treated by salt restriction.

The use of dextrose solutions for postoperative care, without adequate replacement of losses of electrolytes, has sometimes resulted in similar states of renal insufficiency.
When large amounts of sodium and chloride were lost from the body by other routes (as, for example, by biliary fistulas), oliguria or anuria often developed. In fact, any situation which caused a low concentration of sodium in extracellular fluids, regardless of the total amount of such fluids, appeared to predispose already disturbed kidneys to a depression of renal function, with consequent oliguria and retention of nitrogen in blood. The presence of shock was not a necessary

component of this condition, nor was a state of acidosis or alkalosis, carbon dioxide-combining power of the plasma being usually within the normal range.

With the wide employment of low salt diets in congestive failure and hypertension, and with the often excessive use of dextrose in water for postoperative care, renal insufficiency from this cause may be more frequently observed. As it usually is unrecognized unless looked for specifically, and as adequate replacement therapy will often alter an otherwise fatal outcome, the causes, symptoms and methods for treatment will be described. The term "low salt syndrome" has been suggested by Schroeder (1). It is not the intention of this paper to discredit the combined use of the low-sodium diet, mercurial diuretics, and a liberal fluid intake in the management of the various clinical con-ditions calling for this therapy, i.e., congestive heart failure. To do so would be no more logical than to condemn digitalis because some patients become overdigitalized.

About 70 per cent of the total body weight (2) (3) (4) is water and this is distributed in two physiologic compartments, 50 per cent in the intracellular and 20 per cent in the extracellular. Water moves freely between these two compartments in response to osmotic force, potassium providing the effective osmotic pressure in the intracellular compartment and sodium for the extracellular. The distribution of these two cations is the chief factor controlling the distribution of body water (3).

The components of normal daily water exchange with some average figures are shown in Table 1. As can be seen, water becomes available from fluids drunk and from food eaten, the latter providing both its water content and water of oxidation as it is burned for energy. In this way the ordinary solid foods of the diet, meat, vegetables, fruit, et cetera, yield about nine-tenths of their weight as water and furnish an important part of the daily total (5).

On the excretory side two important processes require considerable daily volumes. Water is vaporized from the skin and lungs as part of the heat dissipating mechanism, and with-out visible sweating average-sized adults will daily use 1000 to 1500 cc. for this purpose (6). Since an increase in the vapor-ization of water from the skin surface is the safety valve of heat dissipation, hot humid environments may result in the use of up to 5 liters per day by this process. It is important to remember that the vaporization of water goes on even when

The following table No. 1, gives the components of water exchange for the normal healthy adult under average conditions.

TABLE 1

Available Water	cc.	Excretory Water	cc.
1. Fluids drunk - - - - - - -	1200	1. Water vaporized - - - - -	1200
2. Water from food		2. Water of stool - - - - - -	100
a. Water content - - - - -	1000		
		3. Water of urine - - - - - -	1200
b. Water of oxidation - - -	300		
	2500		2500

COMPONENTS OF NORMAL WATER EXCHANGE

available water is low in amount and other water needs therefore suffer greater restriction.

The second important process by which water is spent is through the kidneys employing water to excrete waste materials in solution, and they do so with the amount available after the vaporization loss has been cared for. In this way the urine output is in most cases a good index of a satisfactory water balance.

The third normal water loss, that of the stool, is insignificant and is seldom much more than 100 cc. daily.

To prevent a rapid depletion of the water in the body a knowledge of the water needed for 24-hour periods is fundamentally important. An adult taking nothing by mouth has about 300 to 500 cc. of water available from the water content and water of oxidation of his own protein, fat and carbohydrate which is burned for energy (2) (4). It is better not to count on this water but to provide the patient with sufficient to cover the two continuous daily losses, i.e., the water spent for vaporization and for urine.

From special studies it is known that a normal adult patient in a comfortable environment will vaporize about 1000 to 1500 cc. per day (5). For patients having an extra load on the heat dissipating mechanism, as by fever, hyperthyroidism or a hot humid environment, one should allow 2000 cc. for this process. For continued marked perspiration much more water may

be so lost and figures up to 5000 cc. daily have been obtained in the uncomfortable top weather conditions (7). By noting the presence and degree of sweating and the coincident low urine output the careful observer will have no difficulty in allowing more water for the vaporization process.

A satisfactory urine output for the majority of patients is 1000 to 1500 cc. per day (8). As can be seen from Table 2, it is two to three times the minimum and will allow for a moderate specific gravity in most instances. Wangensteen (10) and Blalock (11) also recommend these volumes as satisfactory urine outputs for the average surgical patient.

More attention should be payed to the concentration of the urine. A specimen with a specific gravity close to 1.030 denotes excellent kidney function, and conversely an output of low fixed gravity comes from poor function. Table 2 shows that increasingly greater amounts of urine are needed as the kidneys ability to concentrate and the specific gravity becomes less. The individual with very poor concentrating ability may be able to get rid of his daily waste materials and keep out of trouble with urine volumes of 1500 to 3000 or more cubic centimeters daily. Similarly, individuals with a retention of nitrogenous wastes or excesses of electrolytes and organic acids may need 1500 to 3000 cc. of urine daily to correct these abnormalities.

In general the daily water requirements of surgical patients can be summarized (8) as in Table 3.

TABLE 2

Status of Kidneys	Maximum concentrating ability Specific gravity	Minimum water needed cc.
Normal	1.032 to 1.029	483
Diseased **	1.028 to 1.025	595
	1.024 to 1.020	605
	1.019 to 1.015	850
	1.014 to 1.010	1439

* Calculated from Lashmet and Newburgh (9)

** Chronic nephritis, pyelonephritis, renal tuberculosis, et cetera

THE MINIMAL AMOUNT OF WATER NEEDED TO EXCRETE
#% GRAMS OF WASTE MATERIALS

TABLE 3

Simple Case	cc.
Water for vaporization	1000 to 1500
Water for urine	1000 to 1500
	2000 to 3000
Complicated Cases	cc.
Water for vaporization (with sweating, fever, hyperthyroidism, or hot humid environment)	2000 +
Water for urine	1500 +
	3500 +

DAILY WATER REQUIREMENTS OF SURGICAL PATIENT

The kind of parenteral fluid needed to provide water for vaporization and for urine is not salt solution, but water, with dextrose and/or a protein hydrolysate added for nutritional needs.

There is no data on hand to prove or disprove the thought that generally a few grams of sodium chloride should be given daily to patients having no abnormal electrolyte loss but requiring nutritional substance parenterally. It is true that if a patient can take food orally his taste desires would normally include some sodium chloride. It is not illogical then if sustenance depends on parenteral methods to give a small amount of sodium chloride daily. Butler and Talbot (12) place the normal daily allowance at 1 gm. for infants, 3 gm. for children and 6 gm. for adolescents and adults. Conveniently about 5 gm. of sodium chloride can be given daily to adults by 500 cc. of physiological saline or Ringer's solution, or a liter can be given every second day.

Dehydrated patients present a special problem in fluid balance because they have a deficit, and to make up for this deficit they need: (1) More than daily maintenance amounts of water; and (2) Water plus electrolytes.

Electrolytes are of great consequence to the body (3) for they form a most important part of the fluids that diffuse through and around all tissue, and they are responsible for practically all of the total osmotic pressure of the body fluids. In the extracellular compartment, which can be subdivided into the vascular

and the interstitial spaces, sodium, chloride and bicarbonate ions are of greatest abundance while potassium, calcium, magnesium, sulphates and phosphates are in lesser amounts. In dehydration the loss of fluid volume is greater in the extracellular compartment, though not invariably so, and considering that its fluid is the circulating medium that brings every kind of nourishment to the cells, takes away all waste materials, provides the digestive juices and furnishes water for heat dissipation and for urine, it is not surprising that an appreciable loss of this fluid produces profound effects.

The following several pages will be devoted to a listing and discussion of the causes of the salt depletion syndrome.

1. Dietary - Possibly the simplest way to deplete the body of salt is to decrease the intake in the diet. The ordinary diet supplies about 10 grams of salt daily. In dietary regimens that are designed to deplete the body of salt, the intake is often restricted to 1 gram or less. Such a restriction is fairly difficult to obtain and special dietary procedures may have to be devised. Also the unsavoriness of such a diet makes it unpalatable and this, no doubt, accounts for the reason that more serious consequences do not occur more often in its use.

Rigid, uncontrolled salt restriction as a means of therapy for hypertension may prove disastrous. Schroeder (1) has described patients who developed uremia during salt depletion therapy of hypertension. Six patients were observed by Holley and McLester (13), who developed uremia while under treatment for hypertension, using salt deprivation measures. In these patients the presenting symptoms were those of uremia. There was usually a history of severe salt restriction in the diet continued over a long period of time. It was not uncommon to obtain a history of decreased urinary output occurring for several weeks before the patient began to show other signs and symptoms of salt depletion.

Determination of serum chloride on admission usually, but not invariably, showed a marked reduction of this value. The

decreased extracellular fluid volume usually associated with this state may give a false normal value only to be decreased sharply on rehydration regimens. Severe acidosis and uremia were present. Serum sodium values paralleled those of the chloride. In all cases, examination of the urine revealed a markedly diminished chloride excretion.

Institution of therapy with hypertonic salt solution brought about a prompt reversal of symptoms. To prevent this serious complication in patients subjected to salt-free regimens, it may be wise to require frequent blood urea nitrogen determinations. A simpler method would be to follow these patients with periodic determinations of urinary chloride excretion values. Simply measuring the urinary output may be helpful. A marked fall in the urinary volume not accompanied by a decreased intake may mark onset of renal failure.

During the summer months in a hot climate the additional loss of salt from the skin may add to the salt deprivation already being maintained by the dietary restriction.

2. Loss of Salt from the Gastrointestinal Tract -

a. Ileostomy - Loss of secretions from the gastrointestinal tract may seriously deplete the body of salt. Certainly a part of the debilitation associated with ileostomy can be ascribed to the loss from the body of this important molecule. These patients frequently complain of weakness, apathy, listlessness and anorexia. Muscle cramps may be an annoying symptom. During the

summer months, with the added excretion of salt in the sweat, the possibility of renal failure is a recognized hazard. Holley (14) reported one such case. This patient had had an ileostomy performed in the courseof treatment for ulcerative colitis. Several months after this operation she was seen in obvious renal failure. Her serum chloride was decreased. Treatment with hypertonic salt solution was followed by rapid improvement. Ingestion of large amounts of water or electrolyte poor fluids will produce a similar situation as described above.

b. In ulcerative colitis itself, or in severe diarrhea as is seen in cholera, where large amounts of fluid are lost from the gut, serious derangement of electrolyte balance may occur. It is plausible that at least a part of the debilitation seen in these unfortunate victims is associated with loss of salt from the body.

c. Colostomy - The electrolyte and fluid loss in fistulous drainage from the large intestine is much less than that seen in similar conditions involving the small intestine. The loss of salt from such a drainage may be only minimal, but when combined with thatof other salt depletion measures, such as severe sweating, or ingestion of electrolyte poor fluids, symptoms of salt depletion may occur. Muscle cramps, weakness and apathy have been noted in some of these patients, especially during the summer months. During hot weather it might be wise to supplement the diets of these individuals with additional salt to

prevent the occurrence of such symptoms.

3. Removal of Fluid from Serous Cavities - The removal of large amounts of electrolyte containing fluid from a serous cavity will reduce the extracellular fluid volume and deplete the supply of electrolytes and this, in turn, especially if frequently repeated, will producethe syndrome complex seen in a primary salt deficit.

A salt depletion syndrome has been produced experimentally in dogs. Elkinton (15) injected intraperitoneally 150 cc. of a 5 per cent dextrose solution per kilogram of body weight and withdrew the same amount of fluid four hours later. Within four hours, symptoms of salt depletion were produced. The clinical picture of this syndrome simulated that of adrenal cortical insufficiency. The symptoms included apathy, anorexia and nausea. Thirst was not a prominent feature; cramps of muscles and abdominal pain appeared to be outstanding symptoms; cardiac output was decreased; arterial pressure was low; circulation time was prolonged, and peripheral resistance was elevated.

The removal of large amounts of fluid from the abdominal cavity, as is often done in cirrhosis of the liver, seriously depletes the extracellular fluid of its electrolyte content. The fluid of the extracellular compartment then becomes relatively hypotonic, and therefore, water does not leave the intracellular space as it does in primary water depletion. In the latter syndrome, water is furnished by the intracellular compartment,

so that the hypotonicity of the extracellular fluids is diminished. If water is then administered to the patient with salt deficiency, fluid may actually enter the intracellular space. This increases the depletion of the extracellular electrolytes and results in an exacerbation of the symptoms.

After the report of the above experimental work, Holley and McLester (16) studied two patients with decompensated cirrhosis of the liver who displayed symptoms similar to those described in the salt deficiency syndrome produced in dogs. The occurrence of these symptoms was noted after the repeated removal of large amounts of ascitic fluid.

As a rule the treatment of the ascites of cirrhosis of the liver has been unsatisfactory. A recent report tells of improvement following the institution of low salt diets in 12 of 13 patients who had cirrhosis of the liver with increasing ascites (17).

Salt appears to have a priority in the production of the ascites. Nevertheless, the concentration of sodium in the serum is usually slightly depressed, rising with improvement and spontaneous diuresis (18). There is a tendency to retain water in excess of salt.

Since the membranes of all the cells of the body are freely permeable to water, the exchange of fluid between extracellular and intracellular compartments is controlled by the effective osmotic pressure of the extracellular fluid, which is

usually synonymous with the concentration of sodium salts in this fluid. It follows that the state of hydration of the cells is independent of the volume of fluid in the body, depending only upon the concentration of sodium in the extracellular fluid. When sodium rises, the cells five up water and contract; when it falls, the cells take up water and swell. Sodium is, therefore, the instrument by which the distribution of water in the body is regulated (19).

When the intake of salt was limited to less than 1 gram daily, the accumulation of fluid in the abdomen ceased and paracentesis was no longer necessary (17). Except in one patient the diet was well tolerated for more than three months. In this one patient, nitrogen retention developed andthe diet was discontinued; it was thought possible that a decreased renal glomerular flow as a consequence of decreased sodium content in the extracellular fluids was responsible for the uremia. In the other 12 patients, Holley (16) assumed that the improvement was due, not to a decrease in sodium, but to a conservation of body protein incident to the discontinuance of paracentesis. This resulted in a rise of the serum albumin level in each case.

Mercurial diuretics have been used to promote diuresis in cirrhosis with ascites. Although this method is of only limited value, it is used routinely in some clinics. The mercurial diuretics enhance the excretion of sodium chloride from the body and thus decrease the tendency for the formation of edema. On-

which specific ion the mercurial diuretic has its primary (20) inhibiting effect has long been a controversial point.

Excretion of the sodium as well as that of the chloride ion is enhanced. The evidence appears to favor the view that the primary inhibiting effect of the diuretic is on the chloride ion, but sodium and potassium as well as chloride are carried out in the urine.

The removal of large amounts of isotonic fluid from a serous cavity will seriously deplete the plasma of electrolytes; this, in turn, especially if frequently repeated, will produce the syndrome complex seen in primary salt or sodium depletion. It seems reasonable, therefore, for one to assume that the rigid limitation of sodium chloride intake combined with the increased excretion of this electrolyte by mercurial diuretics, will produce such a syndrome. The production of this syndrome may explain the disastrous results that sometimes follow repeated removal of large amounts of ascitic fluid.

Repeated removal of electrolyte containing fluid from other serous cavities will produce a like reduction of the salt content of the body. The development of such a syndrome has been observed after repeated removal of fluid from the chest cavity (14). In this case, an accumulation of fluid in the thorax seriously embarrassed the respirations of the patient. The patient had a diagnosis of lymphosarcoma which principally involved the lymph nodes of the mediastinum. Repeated

thoracenteses, with removal of large amounts of fluid from both pleural cavities, became necessary. After several days of such treatment the patient complained of listlessness, apathy and weakness, together with a persistent headache. Muscle cramps were very prominent. Oliguria and resultant uremia ensued. The patient was found to have confirmatory evidences of salt deficit. Treatment with 5 per cent salt solution rapidly brought about improvement.

4. Loss of salt through the skin - Generally the insensible loss of salt from the body by way of the skin is negligible. However, with severe sweating large amounts may be lost. Apparently, though, the body is able to economize in the face of a salt deficit, decreasing its content in the sweat as well as its excretion in the urine when the serum concentration falls below a critical level.

There is a well recognized syndrome among stokers who develop symptoms of salt depletion while working in excessive heat. These consist of cramps in the abdomen and large muscle groups. In these cases after profuse sweating, the intake of electrolyte-poor fluids cause them to develop cramps and colic, signs of water intoxication referable to hypotonicity of the body fluids.

Animals or men chronically depleted of salt will drink enough water to maintain the body fluids within reasonable limits even at the expense of persistent hypotonicity (21) (22).

It is now generally well accepted that the addition of salt to the water and diet will successfully prevent the onset of these symptoms.

5. Renal origin - By far the largest quantity of salt is excreted from the body by way of the kidney. This organ is of primary importancein maintaining salt balance. The kidneys appear to be able to decrease excretion of salt when the plasma level falls below normal. This regulation of output of salt is undoubtedly under the influenceof the hormones of the adrenal cortex.

a. Adrenal Cortical insufficiency - A large part of the symptom complex seen in Addison's disease is due to the electrolyte disturbance brought about by the loss of the sodium and chloride ions from the extracellular fluid. With a plasma salt deficit the renal tubular epithelium is normally stimulated to reabsorb sodium and chloride from the glomerular filtrate. In the absence of the adrenal cortical hormonesthe mechanism is not effective and the body is rapidly depleted of salt.

b. Chronic Glomerulonephritis - The use of salt depletion procedures have not been found to be satisfactory in the dietary treatment of chronic glomerulonephritis. The individuals very early show signs of salt deficiency. Renal failure is a common occurrence. Ironically, McLester (23) warned of such complications in 1922. In his cases of chronic glomerulonephritis the use of salt-free diets was followed by uremia. Based upon this

work and the observations on out patients, Holley (14), believes that severe salt restriction is unwarranted in chronic glomerulonephritis. Still another similar syndrome has recently been described by Thorn and his co-workers (24). This isthe so-called "salt-losing nephritis." This rare disease syndrome is found in terminal glomerulonephritis and is pesumed to be due to absent or inactive renal tubular epithelium. Although normal amounts of cortical hormone are produced, their site of action is lost. Sodium chloride is, therefore, excreted from the body in the face of a plasma salt deficit. Even though the adrenal gland is intact, an Addison-like syndrome is precipitated. The administration of desoxycorticosterone has no effect in the restitution of this imbalance, but salt added to the diet may cause at least a temporary improvement in these patients.

c. Lower nephron Nephrosis - Destruction of the tubular epithelium, such as is seen in lower nephron nephrosis, may present a similar problem. In this disease process the damaged renal tubular epithelium usually requires approximately two weeks for regeneration, that is, if death does not supervent. Early after the cells regenerate there is marked diuresis with a resultant loss of excessive amounts of electrolytes from the body (25). Apparently the renal epithelium at this time is not responsive to the action of the salt-maintaining hormone necessary for electrolyte balance. Therefore, during this period adequate amounts of sodium chloride as well as other electrolytes must be

provided. Undoubtedly a failure to replace the lost electrolytes may account for some of our fatalities in this syndrome.

d. Mercurial diuretic administration - Profound electrolyte imbalance may be produced by mercurial drugs administered to promote diuresis.

In some cases there is depletion of the salt content of the body's extracellular fluid. These drugs presumably inhibit the reabsorption by the renal tubules of sodium chloride from the glomerular filtrate. The salt is excreted along with large amounts of water in the urine.

Patients under treatment with drugs, especially if they are being treated simultaneously with salt-free diets, may develop symptoms of salt deficiency. The clinical picture presented may beone of oliguria, acidosis, uremia, and static or increasing edema, in spite of large doses of mercurial diuretics administered for the relief of the congestive failure. Generally these have been patients on a rigidly controlled salt-free regimen supplemented by mercurial diuretics (14). Schwartz and Wallace (26) in extended balance studies carried out on six patients with congestive heart failure stated that usually following two or three daily mercurial diuresis the patients became hypochloremic, alkalotic and refractory to further administration of the drug.

Young persons, particularly those with rheumatic heart disease, not uncommonly receive hundreds of injections over many

years without serious reaction. However, particularly in the elderly age groups, diuresis may be followed by asthenia, apathy, somnolence or restlessness, anoréxia, confusion, disorientation, drop in blood pressure, fever, stupor, coma and even death. The blood urea rises andthe chlorides fall. This may be true even of injections given at intervals of several days.

During mercurial diuresis it can be demonstrated that sodium, potassium, calcium and chlorides, in addition to water, are excreted in increased amounts. With such large quantities of fluid excreted during intensive diuresis, the possibility of potassium depletion must be considered very real.

An elevation of blood urea nitrogen is present and presumed to be produced by diminished glomerular filtration and nitrogen or water imbalance. The exact mechanism which obtains in mercurial diureses is obscure but it may be related to some initial renal involvement.

Salt depletion and dehydration reactions do not occur so frequently in young patients with rheumatic heart disease as in elderly arteriosclerotic or hypertensive patients. Certainly in the latter, dehydration and salt depletion are of dire prognostic significance and may contribute directly to a fatal outcome. This is doubtless the result of the presence of unrecognized renal damage in the elderly group. Another factor in producing symptoms probably is the marginal status of the cerebral blood flow in elderly patients with arteriosclerotic and hypertensive cardio-

vascular disease.

In three cases reported by McLester and Holley, they observed increasing edema, even though large amounts of mercurial diuretics were being administered (28).

These cases no doubt, in the past have been labeled "intractable heart failure." The administration of hypertonic saline is lifesaving.

The primary cause of this syndrome seems to bethe depletion of sodium and chloride from the extracellular space (1). This deficiency can be produced by dietary deprivation or by the excessive loss of this salt after diuretic therapy. Sodium and chloride are the principal electrolytic components of the extracellular fluid, and any change in their concentration will presumably disturb the established equilibrium between this space and that of the larger intracellular fluid compartments (29). When there is depletion of this salt the extracellular fluid becomes relatively hypotonic.

As this change takes place, it should follow that the extracellular fluid volume becomes difficult to maintain, the fluid being attracted into the intracellular fluid space by its relatively high electrolyte concentrations. Thus, the extracellular fluid volume falls and the peripheral blood becomes concentrated and increasingly viscous. As a direct result of these changes, the effective renal glomerular flow diminishes and nitrogen retention ensues. Obviously this is more likely to occur

in a patient with preexisting renal impairment (28).

As the syndrome progresses, fluid enters the intracellular space, with resulting engorgement of this space. This explains partly the increase in weight which occurs after salt depletion. Dock (30) has offered an explanation of this paradoxic phenomenon of increasing edema after salt depletion by assuming that the mechanism which initiates maximal reabsorption of sodium by the renal tube also evokes maximal water reabsorption, and that this occurs even after sodium depletion has robbed the body of considerable electrolyte. Sodium excretion normally equals sodium ingestion, with a lag of some days in the establishment of equilibrium when the intake is raised or lowered. Sodium excretion in sweat and urine falls markedly when sodium intake is restricted or sweating has been profuse. If serum sodium is reduced by diet at a time when the mechanism for fluid retention is being powerfully stimulated by severe heart failure, edema increases or remains stationary and uremia develops. Salt administration then may be essential to prevent death. Fortunately this does not occur very often.

Under the conditions described, often attributed to "intractable heart failure," the administration of hypertonic salt solution may be lifesaving. Large amounts must be given to replace the seriously depleted extracellular fluids. At times, 50 to 75 grams of sodium chloride have been given before improvement became apparent. The onset of diuresis soon after administration

of the salt heralds the establishment of normal fluid equilibrium (28).

Soloff and Zatuchni (31) have shown that patients with hypertension or with congestive heart failure who, while receiving intensive therapy with mercurial diuretics and a diet extremely poor in salt experienced symptoms that are very similar if not identical with thoseof salt depletion as seen in the noncardiac patient who is subjected to considerable loss of sodium during a short interval.

The recognition of the syndrome of hypoatremia in persons with congestive heart failure and with hypertension following the institution of a salt-poor diet and the use of mercurial diuretics is not new. For a decade following the introduction of these powerful diuretics many papers appeared in the literature emphasizing the potential dangers of this type of therapy with particular reference to salt depletion and dehydration. Thus, Binger and Keith (32) reported that, of 216 persons with heart failure so treated, an increase in blood urea nitrogen developed in 89. Many of these patients appeared more intoxicated after diuresis than when they were edematous. Poll and Stern (33) observed the symptoms of weakness, restlessness, mental confusion, apathy and even coma and death following excessive diuresis. Klinghoffer (34) observed nausea, anorexia, muscle cramps and vascular collapse. Evans (35) was able to abolish the symptoms by stopping the use of

diuretics and increasing fluids. DeGraff and Nadler (36) in their review of the toxic effects of mercurials in human beings, mentioned the occurrence of chloride depletion and azotemia after diuresis.

It would appear that, if untoward effects of dehydration and desalting therapy were observed soon after the introduction of the mercurial diuretics, they should be more prevalent today, not only because the mercurials are used more frequently and in larger doses today but because diets are available with a much lower sodium content now than at any other previous time. They believe that the untoward effects are more prevalent and that their non-recognition is due to preoccupation with the concept that congestive heart failure can exist only in the presence of excessive sodium retention.

The water and salt mechanisms of the body are disturbed in congestive failure. Merrill (37) has shown that at least in some instances of cardiac failure glomerular filtration is diminished and tubular reabsorption of sodium is increased. It has not been shown whether glomerular filtration is decreased because of a uniform decrease in filtration in each glomerulus or whether there are less glomeruli active at one time. Burch (38) has shown that mercurial diuretics reverse this process of sodium retention and cause a disproportionately greater excretion of sodium. As the time approaches when there is no longer sodium retention, the salt-poor diet exerts a severe strain on tubular

cellular function. Newburgh (39) recently reemphasized that a salt-poor diet may require work of the tubular cells that they are incapable of performing. If this occurs, salt leakage continues, drastic dehydration occurs, uremia and the picture of shock may appear.

e. Renal loss of salt after severe retention of urine - Relief of severe urinary retention may be accompanied by a marked loss of salt from the body. This loss may be continued for several days after the urinary obstruction has been relieved. In addition to the initial shock accompanying decompression of the overdistended bladder, symptoms caused by serious loss of salt may occur.

Moyer (40) has described such cases in which profound symptoms of salt depletion occurred after such procedures. These symptoms were promptly relieved by the administration of salt.

No doubt the production of this profound electrolyte disturbance accounts for some of the so-called "reactions" encountered after these procedures.

6. Fluid replacement therapy - The use of untravenous fluids has become so routine in a clinical practice that serious electrolyte imbalance may be produced if due care is not exercised in evaluating such therapy.

Holley reports the observation of a salt depletion syndrome in a patient being treated for diabetic acidosis. On admission

this patient was markedly dehydrated. After adequate insulin therapy a program of rehydration was undertaken. Response to the therapy at first was excellent. Unfortunately there was injudicious use of large amounts of glucose in distilled water. The patient became progressively more somnolent and listless. Oliguria and later anuria developed. Prompt recognition of a low salt syndrome brought about early remedial therapy (14).

The symptoms and signs of salt depletion are unfortunately nonspecific and may occur in many other conditions (41), such as irreversible myocardial insufficiency, fresh coronary occlusion, exacerbation of a rheumatic carditis, pulmonary infarction, true renal insufficiency, cerebral vascular accident, excessive sedation or overdigitalization. The picture of this syndrome is also similar to that seen in patients with adrenal cortical insufficiency. When a patient being treated on a regimen aimed at lowering the sodium content of the body begins to fail, one must decide whether the downward course is due to one of these conditions or to salt depletion—or both.

In order to make the diagnosis of salt depletion, the condition must be specifically looked for and the diagnosis confirmed by appropriate laboratory procedures. One should not be preoccupied with the concept that congestive failure can exist only in the presence of excessive sodium retention.

Commonly, the initial symptoms are drowsiness, lassitude, and weakness. These may be followed by anorexia and sometimes vomiting, muscle cramps, restlessness, confusion, delirium, shock, coma and death. Tetany has been reported—also the precipitation of grand mal seizures in epileptic patients given mercurials. Cerebral thrombosis and hemiplegia have been attributed to the profound diuresis, blood pressure drop, and increased blood viscosity subsequent to the injection of mercurials. Uremia commonly occurs and is often the presenting

symptom. No doubt this occurrence is due to the progressive renal failure seen in all of these patients. A decreased effective glomerular flow consequent upon the fall in the extracellular fluid volume that results from salt loss probably explains this change in most of these cases (42).

The loss of the electrolyte content of the extracellular space is manifested by marked changes in the circulating blood. Osmolar deficit may be associated with decreased or increased extracellular fluid volume. In patients with osmolar deficit and hypovolemia, the peripheral blood shows hemoconcentration and the plasma proteins may be found to be elevated. Serum chloride and sodium values may be normal or only slightly lowered. The cardiac output falls and the blood flow through the kidney is reduced. Peripheral resistance may be elevated, probably as a compensatory mechanism to assure adequate blood supply to vital organs (29). The concentration of urea rises in the blood, but practically disappears from the urine. Manifestations of uremia and acidosis develop. In these patients physical examination reveals evidences of dehydration. The tongue and skin are dry and the skin loses its elasticity.

In other patients with osmolar deficit a normal or increased extracellular fluid volume may exist. In these, the changes in the circulating blood may be found to be just opposite to those found in the hypovolemic state. There is no evidence of hemoconcentration. The serum sodium and chloride values may

reach very low levels. The extracellular spaces become engorged with electrolyte-poor fluid. Edema increases and renal failure ensues.

The specific signs and symptoms to be looked for in the development of the low salt syndrome are:

1) a successive depression of urinary volume occurring during three to five days.

2) a depression of urinary chlorides to negligible quantities (which does not increase after injection of mercurial diuretics).

3) a rapid progressive gain in body weight.

4) an elevation of the non-protein nitrogen content of the blood.

5) a fall in the plasma levels of chloride and sodium.

6) occasionally an elevation of the cardiac rate.

Symptoms of which the patients complained were (1) drowsiness, weakness and lethargy (often wrongly attributed to sedatives), (2) loss of appetite sometimes with thirst, (3) nausea and occasional vomiting, (4) occasionally abdominal or muscular cramps and (5) the secondary symptoms of an increase in extracellular fluids when edema was already present.

In all cases observed in the literature there was evidence either of some degree of organic renal disease, usually without renal insufficiency, or a functional renal disturbance such as that associated with congestive failure. In chronic

glomerulonephritis with moderate renal insufficiency a similar situation often developed. Although spontaneous recovery sometimes occurred, partial renal shutdown usually persisted until death. Reversal of the process as soon as it was detected was considered important; permanent functional changes probably occurred as the condition became established, against which treatment was often useless.

The treatment of salt depletion is, logically enough, salt replacement. The manner of giving the salt, however, requires some comment. If only a small amount of salt is needed, it may be given by mouth. In severe cases where oliguria or anuria, together with nitrogen retention and the symptoms of water intoxication are present, the sodium and chloride concentrations of the extracellular fluid must be rapidly restored to relatively normal levels. Schroeder (1) strongly advocates the rapid restoration of the concentration of sodium and chloride in extracellular fluids to relatively normal levels by intravenous injection of hypertonic solutions of sodium chloride (5 or 6 per cent). His rationale is as follows:

1. The whole extracellular fluid mass contains an amount of sodium and chloride insufficient to maintain normal osmotic equilibrium. Probably intracellular fluids are increased. The net result is overhydration.

2. The most rapid method of restoring the concentrations of sodium and chloride to normal is to administer salt without water. Any water given would decrease the increment between the concentration of salt introduced into the body and the concentration of salt introduced into the body and the concentration present in extracellular fluids. For example, if body fluids contain a concentration of 75 milliequivalents per liter of chlorides and 120 milliequivalents of sodium, and a value of 100 and 145 respectively are desired, it is obvious that the replacement of

the lacking 25 milliequivalents per liter of sodium and chloride will not readily be accomplished by the administration of isotonic (physiologic) sodium chloride solution (154 milliequivalents per liter). So much solution would be necessary that extracellular fluids would be decidedly increased. Even one liter of isotonic sodium chloride solution per liter of extracellular fluids would increase the concentration of sodium chloride in blood and tissue fluids by only 12.5 milliequivalents; two liters of saline solution per liter of extracellular fluids would be necessary to restore the deficit. This amount is obviously impossible to give to any subject whose kidneys are not excreting water. Therefore, the more concentrated the saline solution, the more readily will the deficiency be made up. By experiment it was found that intravenous administration of 5 or 6 per cent sodium chloride solution could be tolerated if given slowly, the venous pressure rising only slightly, if at all.

3. Although salt can be given by mouth, the amount usually necessary to restore electrolyte equilibrium may be large (20 to 40 Gm.); this quantity can produce gastrointestinal disturbances and may have an erratic rate of absorption. The intravenous route is therefore preferable, although additional amounts may be administered in food or capsules.

4. Serious consequences resulting from the slow intravenous injection of hypertonic saline solution into a patient already exhibiting a high venous pressure and overhydration are

theoretically not to be expected. Injected sodium chloride leaves the blood fairly rapidly, diffusing into extravascular fluids, and probably contributing little to an increase in blood volume except momentarily and until equilibrium between blood and tissue fluids is established.

5. It was found by experiment that diuresis could be initiated when the lacking concentration of salt was restored, cardiac function occasionally improving.

The amount given depended on a calculation of the deficit in plasma, in estimated interstitial fluids and in accumulated edema. Since the kidneys of cardiac patients are deranged but can put out water more readily than salt, reestablishment of their normal balanceof sodium chloride was made slowly so as not to "over-shoot." Normal extracellular fluid volume was considered as 20% of the body weight. Edema fluid, if present, was roughly estimated from the gain in body weight. Plasma levels of chloride and carbon dioxide-combining power were followed daily; subsequent injections of salt were based on their values. Usually when the plasma level of chloride reached 90 to 95 milliequivalents per liter, diuresis was well established. As a rough approximation, for a 70 Kg. man, 17.1 milliequivalents of sodium chloride (1 Gm.) should be expected to elevate plasma levels one milliequivalent per liter if edema is not present and salt is not excreted.

Tepley (41) reports his cases of salt depletion responded

well to physiologic saline, but that Schroeder's reasoning appears logical, especially in the cases that have progressed to the point of water intoxication.

Duncan (43) states that deficiencies must be made up by the administration of sodium chloride and water in proportions to restore the electrolyte concentration as well as the volume of body fluids. Usually this can be effected by the use of normal salt solution. When the salt has been more greatly depleted than water, reparation may be accelerated by the introduction of an appropriate quantity of hypertonic (2%) solution of sodium chloride. Election of the proper amounts of salt and water may be facilitated by analyses of the serum for chloride and bicarbonate.

A sample calculation is presented below:

Na	142 meq.	HCO_3	27 meq.
K	5	Cl	103
Ca	5	HPO_4	2
Mg	3	SO_4	1
	155 meq. / Kg. of body water	Organic Acid	6
		Protein	16
			155 meq.

If it is assumed that the sodium concentration is 120 meq. we find that the deficit when 120 is subtracted from 142 is 22 meq. of sodium.

In this calculation we will use the average normal weight of 70 Kg. for the individual. It is assumed that approximately 60 percent of this weight is fluid volume, so 70 Kg. X .6 = 42.0 liters of fluid. Multiplying the 42.0 liters times the 22 meq. deficit of sodium we obtain a total of 924 meq. of sodium needed to replace the deficit. To convert this amount of sodium (in meq.) to grams we multiply by the molecular weight of sodium which is 58 and obtain 53,600 mg. of sodium chloride. This can be converted to 53.6 Gm. of sodium chloride.

Comparing this to the normal amount of sodium in the body we multiply 140 meq. of sodium by the 42.0 liters of fluid in the 70 Kg. individual and get 5880 meq. of sodium as the total amount in the body.

The development of the "low salt syndrome" is illustrated by the following typical cases which have been taken from the literature.

A woman aged 30, weighed 50 Kg. and was afflicted with subacute and chronic rheumatic endocarditis with involvement of the mitral and tricuspid valves. Her extracellular accumulation of edema fluid was estimated at about 8 Kg. Her electrocardiogram showed many ectopic beats from various ventricular foci. Her weight varied little during a control period of three weeks. The intravenous injection of 2 cc. of mersalyl and theophylline solution (salyrgan) caused a urinary excretion of 17 Gm. of chloride calculated as sodium chloride. Three days later the same dose resulted in the excretion of 6.1 Gm. and was followed by progressive diminution of urinary volume, ending finally in oliguria. A later injection of 4 cc. of mersalyl and throphylline solution did not affect urinary water or chlorides. As the patient was ingesting only 1 Gm. of salt per day, the excretion of 23.1 Gm. of salt (395 milliequivalents) accompanied by only 2.2 Kg. of water apparently depleted her extracellular electrolytes. A week later she had retained 3.4 Kg. of water, which further hydrated and diluted her electrolytes. She died of renal and cardiac insufficiency.

A similar situation resulted apparently from the daily intramuscular injection for twenty days of 2 cc. of meralluride sodium solution (mercuhydrin).

A man aged 69 with long-standing chronic congestive circulatory failure received daily intramuscular injections of 2 cc. meralluride sodium solution for twenty days. Except after the first two doses, there was no diuresis; his urinary volume varied usually from 300 to 800 cc. per day but occasionally was as low as 180 cc. He became weak and nauseated, with occasional vomiting; later, considerable drowsiness developed and he complained of cramps in his forearm, calves and thighs. His plasma chlorides were found to be 81 milliequivalents and his carbon dioxide-combining power 32.5 milliequivalents per liter, and there was retention of nitrogen in his blood. He was given 26 Gm. of sodium chloride in 5 per cent solution in two doses without elevating his venous pressure of 260 mm. of saline solution significantly. His plasma chlorides rose to 91 milliequivalents and his carbon dioxide-combining power fell to 27.5 milliequivalents per liter. Moderate diuresis was initiated, after which the nonprotein in his blood became lower.

A man aged 33 had known rheumatic heart disease involving his mitral valve. During convalesence from pneumonia, severe right-sided heart failure developed with general anasarca estimated at more than 15 Kg. of fluid. His body weight had declined only 1.5 Kg. in two weeks in spite of two injections of 2 cc. of mercurophylline and the use of a propietary double salt of calcium theobromine and calcium salicylate. A large discrepancy was noted between his intake of fluids and his

urinary volume, although he had lost only 115 milliequivalents of sodium chloride in his urine. It was not surprising, therefore, to find in his plasma a sodium level of 124.5 milliequivalents per liter, a chloride level of 76.4 and a carbon dioxide-combining power of 27.8. There was retention of nitrogen in his blood (blood urea nitrogen 27.7 mg. per hundred cubic centimeters). He was given 15 Gm. of sodium chloride intravenously, which initiated a diuresis of water in which chloride values were negligible, caused a loss of 3.5 Kg. in weight and resulted in a moderate elevation of his plasma electrolytes (sodium 129.6, chloride 86.4 milliequivalents per liter). When his weight became relatively stationary adrenal cortical extract (eschatin) was given daily. No chloride appeared in his urine, but a moderate water diuresis was initiated with a further loss of 4.8 Kg. in weight. His plasma chlorides rose to low normal values (93 milliequivalents per liter) as this occurred, but he died soon after with 144 mg. per hundred cubic centimeters of nonprotein nitrogen in his blood. Apparently the renal disturbance which he sustained was irreversible, although obvious lesions to account for it were not found at postmortem examination.

In another case, that of a man aged 42 with rheumatic heart disease involving the tricuspid as well as other valves, adrenal cortical extract likewise appeared to initiate diuresis accompanied by a loss of 2.7 Kg. The plasma sodium level, which

was initially 111.1 milliequivalents per liter (chloride 77.2), rose only slightly and the patient died. No extra sodium chloride was given, which may have accounted for his failure to recover. A wide discrepancy between the intake and output of fluids was a constant feature of his course.

It would appear that patients depleted of salt may die with low urinary output, retention or water and dilution of electrolytes. During this state nitrogen is retained, weight is gained rapidly and chlorides disappear from the urine. Mercurial diuretics produce little or no response on urinary chlorides or water. Their excessive use may precipitate this condition when the intake of salt is restricted.

The diuretic and nitrogen-lowering action of hypertonic saline solution has sometimes been dramatic; for example, in the following case.

A man aged 67 with arteriosclerotic heart disease and severe ascites and edema lost over 500 milliequivalents of chloride in his urine in ten days as a result of mercurial and xanthine diuretics. His net loss amounted to 329 milliequivalents. The characteristic symptoms and signs appeared, his urinary output diminishing (to a low of 283 cc. on one day). A transfusion of whole blood (500 cc.) did not initiate diuresis nor did the use of 5 per cent dextrose solution intravenously (1 liter); probably the latter only served furtherto dilute his electrolytes. But the intravenous injection of 255 milliequivalents of salt (16 Gm.)

apparently restored electrolyte balance sufficiently to allow diuresis to begin. Within four days his output increased to well over one liter; however, the chloride output of his urine remained exceeding low and his symptoms disappeared. Although he had gained 2.9 Kg. in weight, the diuresis initiated by salt resulted in a loss of this amount and a further loss of one Kg.

The mechanisms leading to the development of this bizarre form of renal insufficiency are not known. Some toxic action of mercurial diuretics on the kidneys is probably not the predominating factor; a high fluid intake precipitated the state in three instances.

A man aged 65 had ascites and edema resulting from arteriosclerotic heart disease. He had received three injections of mercurial diuretics at five day intervals, which caused a total loss of 465 and a net loss of 243 milliequivalents of chloride. No mercurial compound was given for fourteen days. When the patient's intake of fluids was raised from 1,200 to 2,500 cc. per day for four days his urinary volume failed to increase; in fact, it became slightly depressed. He became drowsy, disoriented and weak. Chlorides in plasma were found to be 73.5 milliequivalents per liter and nonprotein nitrogen 61 mg. per hundred cubic centimeters. Reduction in the intake of fluids was followed by a diuresis of water, negligible quantities of chlorides appearing in the urine, and his plasma chlorides rose moderately. He continued in a hypochloremic state until relieved

by the injection of saline solution and a more liberal dietary intake.

The same case illustrates another point. When the condition is more or less borderline with slight diminution of urinary volume and depression of electrolytes there may be chronic elevation of the nonprotein and urea nitrogen in blood, and the urea clearance becomes depressed. This patient's urea clearance was 46 per cent of normal when his electrolytes were at low normal levels. When his plasma chlorides fell to 73.5 milliequivalents per liter, the urea clearance was 10 per cent of normal and the blood urea nitrogen 67.8 mg. per hundred cubic centimeters. A reversal of the process by the injection of hypertonic saline solution and the addition of salt to his diet resulted in a rise in his plasma chloridesto 93.4 milliequivalents per liter and in his urea clearance to 62 per cent.

This same type of renal insufficiency may follow excessive loss of chlorides as a result of vomiting when replacement therapy has been inadequate.

A woman aged 78 had had partial intestinal obstruction which was relieved by surgical intervention. Oliguria and retention of nitrogen in the blood was a constant feature of her postoperative course, and she was believed to be near death. Replacement of the electrolyte loss by hypertonic saline solution resulted overnight in dramatic improvement. Diuresis became established. The blood urea nitrogen fell to normal levels, and the patient was able to

resume normal activity. That this change was not coincidental is suggested by the rapid onset of adequate renal function.

Of the 11 patients who recovered in Schroeders series (1), either spontaneously or as a result of the injection of sodium chloride solution, four subsequently died in a similar state of renal insufficiency. Provided early treatment was instituted, recovery was rapid when salt was given and slow when it was not. Sometimes a dose much less than that calculated to be ideal began recovery. Excess salt resulted in the accumulation of edema.

The injection of hypertonic sodium chloride solution was not accompanied with adverse symptoms when plasma electrolytes w were low. Venous pressure was always measured simultaneously; occasionally it fell slightly, more often there was no change, but sometimes it rose two to three cm. of saline solution after the first 100 cc. had been given, rising no further. The presence of pulmonary congestion did not contraindicate the injection of the hypertonic sodium chloride solution. When the electrolyte concentration in plasma was low, minimum pulmonary edema was observed in two cases to regress while sodium chloride solution was being injected. Even large quantities of hypertonic saline solution (6 per cent) sometimes failed to elevate venous pressure significantly above an already high value. Diffusion from blood into tissues was rapid, and higher plasma levels were not always maintained. Plasma chlorides were measured in two cases ten to fifteen minutes, ten to twelve hours and twenty-four

hours after the injection. An immediate rise of 7.5 milli-equivalents per liter, caused by the injection of 5 Gm. of sodium chloride, produced one of 3.5 milliequivalents twenty-four hours later. Six grams of salt produced a rise of 7.2 milli-equivalents in ten minutes, but only a rise of 2.1 the next day. Both patients were edematous. Their urine did not manifest a significant increase in total chloride content, although the concentration of a single specimen was increased.

Peters and Van Slyke (44) have discussed the matter of renal insufficiency resulting from sodium depletion in these words:

The nonprotein nitrogen of the blood tends to increase in all conditions in which the fluids of the body are greatly depleted, whether the dehydration results from simple deprivation of fluids or from excessive loss of fluid through vomiting or diarrhea. These increases seem to arise chiefly from oliguria, with accelerated protein catabolism and impaired circulation playing contributory roles. A voluminous literature has sprung up about a condition known as "uremia or azotemia from lack of salt," in which it is implied thataccumulation of nonprotein nitrogen in the blood is a direct response to depletion of the sodium and chloride of the body. Such a theory finds little physiological support. Deficits of chloride and sodium in the body fluids are generally indications of dehydration. . . .

Accumulations of nonprotein nitrogen in the blood in this condition can be eliminated by the administration of enough water to provoke diuresis, although the deficits of chloride and sodium may be aggravated by such therapy. If salt depletion contributes to azotemia at all, it is probably through its injurious effects on bodily functions in general, and especially upon the circulation, not because it has any particularly deleterious influence upon the kidneys. It hasbeen reported that injections of small volumes of concentrated sodium chloride solution are benificial in restoring

the excretory activity of the kidneys; but such salt injections increase the volume of extracellular fluid by abstracting water from the tissue cells, thereby providing more water for the formation of urine.

They have suggested further thatthe elevation of blood urea is "probably only a manifestation of the circulatory collapse which results from sodium depletion."

The syndrome described appears to be a state of renal insufficiency dependent on a disturbance of the normal concentration of sodium chloride in extracellular fluids. It has not dehydration, as absolutely defined, because large storesof water containing dilute sodium chloride solution may be present. It is not dependent on alkalosis, for the carbon dioxide-combining power of the blood may be altered only slightly. It can be initiated by depleting the body of sodium chloride through the use of either mercurial diuretics or other measures, by producing a large discrepancy between the intake and the output of fluid or by excessive loss of salt through abnormal routes. It is often reversible by restoring the concentration of sodium chloride in body fluids to normal, a procedure which can cause diuresis and a return of renal function to higher values. It may accompany but it is not always dependent on circulatory insufficiency; it is usually associated with prior renal disturbance, either functional or organic.

It is probable that the excessive use of dextrose solution

in water without sodium chloride postoperatively contributes to renal insufficiency and initiates the low salt syndrome in elderly patients or in those who already have some renal disturbance of minor degree. The recognition of this syndrome becomes important, because immediate therapy may be life saving. Delay has resulted apparently in irreversible changes in the function of the kidneys.

This condition is apparently the same as one described recently by MacGuire (45), who reported three cases of hypertension associated with congestive failure. On diets low in salt, and in two instances after the use of mercurial diuretics, blood urea levels rose considerably only to fall when salt was added to the diet.

The cases reviewed here demonstrate the variety of diseases in which uremia may be encountered as a response to sodium depletion. It is again emphasized that these are not at all infrequent occurrences and that, in order to avoid such consequences, it is wise to watch carefully the levels of blood urea (or creatinine) in all patients on a sodium depletion regimen, especially in those in the older age groups and in those in whom renal disease is suspected or known to exist.

A related situation may be one reported by Muirhead and Fromm (46), who found dilution of extracellular sodium and chloride in the syndrome of acute renal insufficiency. It is possible that many cases of so-called postoperative, reflex or essential anuria

belong in the group here discussed. Renal failure resulting from the "salt-losing nephritis" of Thorn, Koepf and Clinton (20) may depend on the same underlying mechanism, although the kidneys of their patients were able to excrete large volumes of water. Chabanier and Lobo-Onell (47) have described at length a condition occurring after operations, characterized by hypochloremia and azotemia with low urinary output reversed by the intravenous administration of hypertonic saline solution. Although blood pressure was often lower when this state had developed, shock was not present. The article by Soloff and Zatuchni (31) of this syndrome in congestive failure and in hypertension treated by isotonic sodium chloride solution has been discussed. They did not stress, however, the oliguria which usually accompanies this condition. These observations indicate that there may sometimes be an inverse ratio between sodium and chloride in body fluids and nitrogenous products in the blood; they further suggest some obscure relation between the concentration of sodium chloride in plasma and the ability of the kidneys to excrete nitrogen. It must be emphasized that serious disturbances of acid-base balance were not present.

The mechanism whereby lowered electrolytes contribute to renal insufficiency is unknown. The lowered electrolytes contribute to renal insufficiency is unknown. The lowered urea clearance and elevation of the blood urea suggest that renal blood flow is reduced. More exact studies will be necessary to prove this

point. Theoretically, if adequate water is available and plasma is being filtered by glomeruli, normal kidneys should be able to excrete water and retain salt until electrolyte balance is restored. That these kidneys can excrete water to some extent is shown by the two experiments in which adrenal cortical extract apparently initiated a water diuresis. That these kidneys cannot excrete salt is demonstrated by the negligible quantities of chlorides in the urine and the failure of chlorides to appear even when diuresis was stimulated by mercurial compounds.

The normal kidney performs a marvelously exact function of regulating body fluids and electrolytes and maintaining acid-base equilibrium. The abnormal (hypertensive, cardiac or aged) kidney may be deficient in some of these functions. Whether the low salt syndrome occurs only in the presenceof renal disease or renal functional disturbance and never develops when the kidneys are perfectly normal cannot be stated at this time. In every case history reviewed the kidneys were diseased functionally from congestive failure or anatomically from other causes.

Congestive circulatory failure is the result of a renal disturbanceof salt-and-water-regulating mechanisms. The syndrome here reported represents in respect the advanced stage of that disturbance in which neither salt nor water is excreted. The deficiencies of the cardiac, diseased or aged kidney, therefore, may contribute to a precarious state of water and salt balance which can be disturbed by well meant therapeutic measures into

fatal deficiencies of other functions.

The mechanism of the partial renal shutdown is not understood, but the sequence of events may be somewhat as follows:

1. Salt depletion from mercurial diuretics (48), excessive hydration due to a high intake of fluids or, perhaps, spontaneous failure of the kidneys to excrete water occurs.

2. Some stimulus resulting from an abnormally low sodium chloride level in plasma or extracellular tubular reabsorption of both salt and water. Water moves into cells, disturbing their function.

3. Urinary volume is diminished and nitrogen retention begins.

4. Continued intake of fluids enhances the relative overhydration. The function of myocardial as well as other cells is altered adversely by this dilution.

5. Uremia from renal shutdown develops.

6.. When the proper balanceof sodium and chloride in fluids is restored, conditions become more favorable for cellular function and the kidneys again begin to excrete water and nitrogen.

The return of renal function probably is not dependent on a restoration of circulatory efficiency through increases in the blood volume, for venous pressure, a rough indication at least of the state of the blood volume, was not reduced during anuria. Nor is it dependent on adequate levels of blood pressure. Although in some cases the blood pressure tended to be lower, in others there

was little change, while the pressure remained high in some of the hypertensive patients. It is probably not dependent on the abstraction of water from cells to make water available for the kidneys; plenty of water was often available. Cellular hydration in the kidneys, as elsewhere, may have interfered with function, adequate concentrations of sodium chloride removing water from cells and in some manner increasing renal and cardiac function.

The useof hypertonic sodium chloride solution for making up the salt deficit deserves comment. The useof solutions composed of concentrations of sodium chloride necessary to overcome deficits is much more logical than is the routine employment of isotonic sodium chloride solution. When overhydration is present and relative acid-base balance is undisturbed, sodium chloride in concentrated solution should be used (1). Concentrations as great as 20 per cent have been advocated. When dehydration is present and there is a water deficit, water should be used. Only when deficits of both are present to an equal degree is isotonic sodium chloride solution the concentration of choice. When acidosis or alkalosis are found, the fluid which is administered should contain anions or cations to make up the deficit. Good kidneys can compensate for errors in the concentrations of electrolytes administered; poor kidneys, or those with disturbed function often cannot. The intelligent use of fluids therefore requires a knowledge of the relative concentrations of electrolytes in plasma and a readjustment of those in the fluids

administered to compensate for deficits. The use of standard concentrations for all purposes is to be deplored.

The hazards of the rigid restriction of sodium chloride in the diets of cardiac patients, used concomitantly with mercurial diuretics, cannot be overemphasized. The low salt diet has proved a valuable adjunct to the management of congestive circulatory failure, preventing the accumulation of edema fluid. However, when agents which act specifically to increase the renal excretion of chlorides are also used, depletion of salt can be expected. Theoretically, thesame situation might occur if the sodium in intestinal fluids were bound by adsorption on to the newer ion-exchange resins (49). If deficits of salt can be produced in the body by these resins the frequent occurrence of this syndrome can be predicted from their use. It therefore becomes obvious that careful attention must be paid to the water and electrolyte balances ofthe body when these disturbances of balances are being treated, and especially when the intake of sodium chloride is severely restricted.

This paper has presented a syndrome of renal failure which results from (a) retention of water and dilution of electrolytes or (b) excessive depletion of body salt, usually by the use of mercurial diuretics. Sometimes this condition can be reversed by the intravenous injection of hypertonic sodium chloride solution in amounts sufficient to restore electrolyte-water equilibrium. This syndrome is not uncommonly seen in congestive circulatory failure.

The literature has been reviewed and the high lights of the syndrome presented along with signs, symptoms and treatment. It is not meant to discourage the use of low salt diets and diuretics in the treatment of these conditions, i.e. congestive circulatory failure, but merely to watch for the development of the reported syndrome and institute immediate treatment.

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