The Correction of Electrolyte Deficits in Cardiovascular-Renal Disease

By F. R. Schemm, M.D., and A. A. Câmara, M.D.

DR. SCHEMM: We are all familiar with the syndrome of sodium depletion and the resultant fall in extracellular fluid volume that occurs among the so-called salt-losing hypertensives and nephritics. Such patients, because of poor kidney function, lose sodium through the urine in excess of their intake of this electrolyte. The symptomatology produced is very much like that seen in Addison's disease: weakness, fall in blood pressure, anorexia, nausea, vomiting and cramps. Today we shall concern ourselves with the more difficult situations arising in patients with the added problem of edema.

A PHYSICIAN: Dr. Schemm, before you go any further, will you please explain the mechanism by which some nephritics and hypertensives become salt-losers? You mentioned that such patients have "poor kidney function," but this phrase is also used to explain the formation of edema.

DR. SCHEMM: I knew that using the ambiguous phrase, "poor kidney function," would lead to this question, and I am glad you asked it.

As you know, in health the volume of the extracellular fluid as well as the concentration of the electrolytes (mainly sodium) dissolved in this fluid are, within narrow limits, maintained constant. This means then that the healthy individual maintains sodium and water balance (i.e., intake equals output) from day to day. We do not need to go into the details at this point, but suffice it to say that the ultimate task of balancing intake against output falls on the kidney tubules. Even on as low a sodium intake as 150 to 200 mg. daily (6.5 to 8.7 mEq.) the normal kidneys are able to maintain balance by a sharp reduction in the urinary output of sodium, i.e., there is virtually complete reabsorption of all the sodium present in the glomerular filtrate. This means that osmotic work is done by the kidney tubules. Now, the badly damaged kidneys of patients with advanced nephritis or terminal hypertension are unable to perform the necessary amount of osmotic work; hence much of the filtered sodium remains unabsorbed as the glomerular filtrate courses through the distal tubules, and the unabsorbed sodium appears in the urine, irretrievably lost to the organism. It is little wonder then that such patients easily get into trouble even with moderate restriction of dietary sodium; for, like otherwise untreated Adisonians, they require supplementary doses of sodium salts to maintain sodium balance. I should like Dr. Câmara to comment on the concept of edema formation.

DR. CÂMARA: I certainly object to the use of the phrase, "poor kidney function," to explain the mechanism of edema formation. The main disturbance in the formation of edema, be it the edema of congestive heart failure, of glomerulonephritis, or of cirrhosis of the liver, is an excessive tubular reabsorption of sodium from the glomerular filtrate, resulting in an abnormal retention or positive balance of sodium, with a secondary retention of water in proportionate amounts such that the concen-
tration of sodium in the edema fluid is usually the same as its concentration in normal interstitial fluid. In other words, the kidney tubules in edema are doing more osmotic work with regard to sodium than they should. It is, then, only in the sense that excessive tubular osmotic work is being done that kidney function in edema may be regarded as "poor."

More recently experimental data have been obtained purporting to show that in some cases of edema, excessive retention of water might be the primary change, followed by increased reabsorption of sodium. We shall elaborate more on these points as we discuss the problems encountered in some of the patients to be presented today.

A PHYSICIAN: Most of the cases of "salt losers" reported in the literature are sodium losers. Are there also "potassium losers" in the same sense?

DR. SCHEMM: Yes, there are potassium losers, and one should be on the lookout for them especially in two situations; (1) cardiac and nephritics, with edema previously responsive to treatment, who become refractory to treatment, and (2) patients with far-advanced kidney disease, some of whom become spontaneous potassium losers.

We have several patients in our series who belong to the first category. In the early course of their trouble, they get rid of their edema on the diuretic regime without developing potassium deficiency. As in normal subjects, their kidney tubules are able to reabsorb selectively the necessary amount of potassium from the glomerular filtrate to maintain potassium balance, even in the face of a diuresis of sodium caused by mercurial administration. Later on, for some unknown reason, the kidney tubules lose the power of selective reabsorption of potassium and a dose of mercurial diuretic causes as much, if not more, urinary output of potassium than of sodium. At this stage the edema becomes resistant, but we have seen such patients respond to treatment again with administration of potassium salts by vein or by mouth.

Let me briefly review with you the case of a 56 year old patient, R. M., to illustrate the situation I have just described.

This woman had severe rheumatic heart disease with a marked degree of mitral and aortic valve involvement. She had suffered from rheumatic fever when she was 18, and had been aware of persistent irregularity of heart action since the age of 32. When first seen in 1949 at age 53, she had been in severe congestive failure for at least two years. The edema readily cleared on the usual diuretic regime. From then on there followed a long series of admissions with a progressively intractable edema. Sodium and potassium balance studies were carried out on each of her many admissions to the Metabolic Unit. It was during the course of a hospitalization in 1950 that marked urinary losses of potassium with mercurial administrations were first discovered. On one occasion, for example, an intramuscular injection of 3 ml. of Thiomerin resulted in a urinary output of 216 mEq. of potassium as compared to 118 mEq. of sodium on the same day. This meant negative balance of potassium especially on certain days when food intake was poor, and was reflected in a drop of plasma potassium to definitely hypokalemic levels (1.9 to 2.1 mEq. per liter). Her edema started to clear up after attention was paid to maintenance of potassium balance which required an intake of 6 Gm. of potassium chloride daily.

Potassium chloride may be given intravenously (2 to 4 Gm. in 1000 ml. of 5 per cent dextrose, depending on the patient's needs) or by mouth. The latter route is preferred whenever the patient can tolerate it. We give it in a capsule, buffered with an equal amount of calcium carbonate. Some patients will complain of burning despite the calcium carbonate; in this event they are given potassium bicarbonate instead. Each gram of potassium chloride supplies 13.4 mEq. of potassium, whereas a gram of potassium bicarbonate yields only 10 mEq. of this electrolyte.

DR. CÁMARA: While working with Dr. Newburgh in Michigan I had the opportunity to study potassium metabolism in a number of advanced cases of renal damage in whom the volume of the glomerular filtrate had been reduced to as low as 4 to 10 liters per 24 hours. Interestingly enough, we found in these patients either normal or low plasma potassium levels, in contrast to the usual reports of potassium intoxication in severe renal disease. The existence of potassium deficiency in these patients was demonstrated not only by the finding of hypokalemia but also by the avidity with which administered potassium was conserved, as shown by potassium balance studies.
A typical case in our series was D. M., a 49 year old man who entered the hospital in stupor following several convulsive seizures. There was severe uremia and anemia. The glomerular filtrate volume as measured by the endogenous creatinine clearance was only 6.6 liters in 24 hours. Retrograde pyelograms disclosed polycystic kidneys. Little improvement was seen following blood transfusions and infusions of dextrose, saline and sodium lactate solutions, but after addition of potassium chloride to the intravenous fluids there was rapid improvement in sensorium and eventual recovery. Unfortunately, the plasma potassium level was not determined prior to administration of potassium chloride, but even after he had received 16 Gm. of it in 36 hours, the serum potassium concentration was only 3.2 mEq. per liter. Thereafter, he received orally 12 Gm. of potassium bicarbonate daily until normal serum potassium levels were attained. This man was able to go back to work as a machinist for one year before he succumbed to total kidney failure.

A Physician: Dr. Câmará, would you classify this patient in the second category of potassium losers that Dr. Schemm previously mentioned?

Dr. Câmará: Definitely. Note that this patient was not on a diuretic regime but had spontaneously developed potassium deficiency. I forgot to mention that he had had anorexia for two weeks prior to admission, making for a poor food intake during that period. Potassium deficiency should have been suspected from the beginning owing to that fact alone.

In patients with advanced kidney disease we have demonstrated that renal tubular secretion of potassium takes place as a compensatory mechanism which prevents potassium intoxication (in normal subjects, about 90 per cent of the potassium in the glomerular filtrate is reabsorbed). This mechanism obviously plays a major role in the development of potassium deficiency when the food intake is poor. Other factors which contribute to a continuing large urinary loss of potassium in kidney disease are impairment of the capacity for ammonia production and reduction in the ability to produce an acid urine, thus necessitating increased excretion of fixed base whenever large quantities of acid ions are presented to the kidneys for excretion (such as follows the administration of ammonium chloride or ingestion of a high protein diet). Usually the loss of fixed base in such a situation consists primarily of sodium. However, we have demonstrated that when dietary sodium is sharply restricted, an internal stimulus for the kidneys to conserve sodium develops, and the fixed base excreted during ammonium chloride administration may then consist almost entirely of potassium.

Dr. Schemm, I am afraid all this talk on potassium has been a digression from what you had originally intended to discuss.

Dr. Schemm: Not at all, Dr. Câmará. These remarks on potassium are by no means a digression; it just shows that sodium and potassium cannot be divorced from each other in any discussion of electrolyte metabolism.

The problem of electrolyte deficits in patients with cardiovascular-renal disease is truly a fascinating and complex one. It is a problem of many facets which anybody interested in this field is bound to encounter. Take, for example, the problem of severe hyponatremia developing in cardiac patients with resistant edema as a result of the use of mercurial diuretics. Here, one is faced with a dilemma: hyponatremia cries out for sodium replacement, while edema interdicts its administration. The problem is, to paraphrase Shakespeare, to give or not to give sodium salts. When the degree of hyponatremia is severe enough to produce symptoms such as mental confusion or even coma, "cogwheel" resistance to passive movement of the extremities, and other symptoms, one is forced to risk worsening of edema and administer sodium salts.

A 65 year old woman, B. S., whom we had in the Metabolic Unit a year ago exemplifies such a problem. She had rheumatic valvular heart disease with mitral stenosis, and possibly a concomitant hypertensive and arteriosclerotic heart disease. She had been in frank congestive failure for two years prior to admission. When she came to the Unit she was orthopneic and had frequent severe episodes of paroxysmal dyspnea. The heart was markedly enlarged and was fibrillating. She had bilateral hydrothorax, hepatic passive congestion, ascites, and deep dependent edema.

Electrolyte balance studies were carried out in this patient as is usually done with edematous patients admitted to the Metabolic Unit. The plasma sodium concentration on admission was 143 mEq. per liter. She received 1 ml. of Thiomerin on the third, and again on the sixth hospital day, with so-
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...ium diuresis but with practically no weight loss. On the twelfth day, she weighed 2.6 Kg. more than she did on the day of admission, despite the fact that she had had the mercurial diuretic twice and a total of 1,350 ml. of chest fluid had been aspirated from both pleural cavities. On that day the patient was in a coma. The plasma sodium was found to have dropped to 118 mEq per liter while plasma potassium was at a normal value of 4.4 mEq per liter.

At this point we felt we were licked unless something drastic were done. The degree of hyponatremia evidently was great enough to account for the coma. We also knew that no further progress with regard to clearing of edema could be made, knowing from previous experience that hyponatremia in itself has an antidiuretic effect.

A Physician: I would like to know if you have found among your patients a particular critical level of plasma sodium at which symptoms begin to appear.

Dr. Schemm: No, there is no such critical level that applies to all the patients. I have seen a patient who was only mildly disoriented at a plasma sodium level of 103 mEq per liter, and, on the other hand, I have witnessed hallucinations and confusion set in with a plasma sodium concentration reduced only to 124 mEq per liter. I would imagine that several factors such as the rate of drop of concentration of plasma sodium and the state of body stores of other minerals (potassium, calcium, magnesium, and others) determine the critical low level of plasma sodium at which symptoms appear.

To go back to our patient B. S., she promptly roused from her coma within a few hours after administration of 24 Gm. of sodium chloride (800 ml of 3 per cent sodium chloride solution) with 200 ml. of molar sodium lactate solution. This infusion gave her a total of 610 mEq of sodium. By the following day the plasma sodium concentration had risen to 148 mEq per liter. Following this correction she responded to three doses of Thiomerin with an edema weight loss of 9 Kg. in the next 11 days during which she received more sodium chloride and sodium lactate solutions both in hypo- and hypertonic forms. The plasma sodium at the end of this particular period was 145 mEq per liter.

A Physician: This all sounds paradoxical to me. In the management of edema we aim at the excretion of excess body sodium which is responsible for the excessive volume of the interstitial fluid, yet in this case, you achieved results by further use of a mercurial diuretic, truly enough, but also by simultaneous administration of sodium salts.

Dr. Schém: There are many aspects of edema that we do not fully understand, to be sure. In the case of patient B. S., our balance studies showed that during the 10-day period when the plasma sodium dropped from 140 to 118 mEq per liter there was a negative sodium balance of 306 mEq. associated with a weight gain of 2.6 Kg. instead of a weight loss. During the succeeding 11 days when sodium replacement was carried out, she exhibited a negative sodium balance of 341 mEq. with a weight loss of 9 Kg. and correction of hyponatremia. I should mention at this juncture that we gave her a course of corticotropin therapy during the second period under consideration, which may well account for the altered favorable response to the mercurial diuretic. We shall discuss corticotropin later in connection with other patients.

Dr. Cámara: The annoying failure of this patient to lose edema despite negative sodium balance during the first period is typical of the behavior of certain badly degenerated or what appeared to be terminal cases that we have seen.

I think this is a good place to elaborate further on the current concepts of edema formation. Dr. Schemm pointed out in the beginning of this conference that the extracellular fluid in health is characterized by constancy of concentration of each of its inorganic constituents, and also by relative fixity of its volume. These two features are under separate control, working through the kidneys which are the final guardians of the “milieu interne.” The reabsorption of sodium is controlled by the adrenal cortical hormone, but the body content of water is governed by the antidiuretic hormone through regulated reabsorption of water. Constancy of concentration of sodium is maintained in health, so that there must be coordinated activity of these functions, causing the rate of reabsorption of sodium to keep pace with the reabsorption of water. At the present stage of our knowledge, we do not know the
ultimate nature nor the seat of this coordinating mechanism.

In edema, whether it be the anasarca of heart failure, the nephrotic edema of glomerulonephritis, or the ascites of cirrhosis of the liver, the organism has become abnormally geared to maintain an excessively large volume of extracellular fluid. However, except in the far-advanced or deteriorated cases, coordination between the two factors which govern renal tubular reabsorption of sodium and of water is still maintained, as evidenced by persistence of normal concentration of sodium in the extracellular fluid, including edema fluid. In the far-advanced cases, be they cardiae, cirrhotics, or nephritics, the stimulus for maintenance of an abnormally large volume of extracellular fluid is so intense that when measures such as dietary sodium restriction and mercurial diuretics are instituted for the prevention of further accumulation and for the elimination of excess body sodium, normal sodium concentration in the extracellular fluid is sacrificed for volume; i.e., such patients do lose body sodium, but retain disproportionately excessive amounts of water, resulting in the picture of edema with hyponatremia.

DR. SCHIEMM: As previously pointed out, hyponatremia in itself has an antidiuretic effect, and so an impasse is reached.

We have tried the trick of simultaneously administering sodium chloride solutions and a mercurial diuretic in the situation just described.

The case of H. M. on one of her admissions to the Unit presented a similar problem in which edema had developed in the face of abnormal electrolyte loss through diarrhea. She was 38 years old, had rheumatic heart disease with a severe grade of mitral stenosis and moderate mitral insufficiency, and had undergone a mitral valvuloplasty a year previously. Even after surgery she had to be kept on a diuretic regimen to keep her free of recurrent edema. Nine days prior to this particular admission she contracted gastroenteritis with frequent loose bowel movements which persisted until admission. Four days after onset she developed an acute upper respiratory tract infection and from then on she became progressively worse, manifesting dyspnea, cyanosis, cough, and culminating in several emeses just before admission. She noted a rather rapid development of edema with a total weight gain of 9 pounds during this episode. On admission she exhibited orthopnea, deep cyanosis, auricular fibrillation with a rapid ventricular rate, marked pulmonary passive congestion, a tender liver that extended 3 inches below the right costal margin, some ascites, and leg edema. There was no improvement during the first hospital day despite a booster dose of digitalis and oxygen and she was even worse the following morning. On this day, plasma sodium and potassium were reported to be 135 and 4.3 mEq. per liter, respectively. She was then given 2 ml. of Thiomerin intramuscularly and later in the day she received 500 ml. of 2 per cent sodium chloride and 1000 ml. of isotonic sodium chloride, making a total of 325 mEq. of sodium. There was a dramatic clinical improvement within a few hours following the two infusions. The following day the weight was unchanged; but with correction of plasma sodium to 143 mEq. per liter, she responded to two subsequent doses of Thiomerin with loss of 10 pounds of edema weight in eight days and maintenance of normal plasma sodium values.

We have administered sodium chloride to edematous cardiac patients in still another situation. These are the patients who become mercurial fast after having lost only about half of their edema. These patients respond again to mercurials and lose the rest of their edema, but only after a "rest period" during which it is best to relax dietary sodium restriction or even give sodium chloride intravenously. During the resistant phase, in spite of the excess volume of interstitial fluid still present, such patients exhibit a sharp drop in venous pressure, oliguria and those clinical evidences of hypovolemia of the blood, so well described by Lyons and Pitts in nonedematous normals who have been given mercurial diuretics. In these cases, we suspect that a too rapid fall in tissue pressure with initial loss of edema had disturbed hemodynamics and caused the development of a seemingly intractable edema.

A PHYSICIAN: I am able to follow your line of reasoning in administering sodium salts to edematous subjects under the circumstances you have just described; however, I am completely in the dark as to the rationale behind the use of corticotropin in patient B. S. who, if I remember correctly, was in congestive heart failure. My instruction in physiology and endocrinology would lead me to believe that corticotropin would only enhance sodium re-
tention and that it would be contraindicated in congestive heart failure.

Dr. Schemm: Unfortunately, or rather fortunately, our experience with corticotropin in congestive failure has belied its known effects on the renal excretion of sodium in normals. You may well realize the fear and trepidation with which we used this hormone for the first time on a case of congestive failure in the spring of 1952. Since then we have had the opportunity to use it in 17 other cases. We have been highly gratified with the beneficial results obtained in 15 of these cases, more so when one considers the fact that the patients on whom it was used were selected on the basis of intractability of edema to the usual diuretic measures (including mercurial diuretics) and/or myocardial insufficiency of a degree sufficiently severe to warrant a classification of "hopeless cases."

Electrolyte balance studies on these patients show that corticotropin does one of two things; i.e., it causes a spontaneous profuse diuresis of sodium starting either on the third to sixth day of its administration (it is given in doses of 15 to 25 U every six hours for 10 to 12 days) or after its discontinuation; and, in those cases where no spontaneous diuresis occurs, it produces an altered response to mercurial diuretics, making the latter effective where they had been completely useless before. Furthermore, apropos our subject today we have seen it in a few instances correct hyponatremia in an edematous subject without necessitating supplements of sodium salts, as was the case with D. K.

This 69 year old man from Canada had had a coronary occlusion eight years previously. He became aware of exertional dyspnea four years, and of dependent edema two and one-half years prior to his admission here. The edema had lately been getting unrelentingly worse despite adherence to a low-sodium diet and the use of oral as well as parenteral mercurial diuretics, the latter having been given as often as three times a week. He was obviously in severe congestive failure when we saw him, having a marked generalized fullness of the body with definite pitting in the dependent parts, moderate ascites, splenomegaly, and a tender liver that was ballotable for 4 inches below the right costal margin. On the third hospital day, a trial dose of 2 ml of Thimerin given intravenously was "rewarded" by a urine output of 500 ml which contained 0.7 mEq. of sodium, and further weight gain of 3.5 pounds. On the fifth day, when corticotropin was started he was much worse, having more edema, persistent oliguria (despite adequate water intake), annoying constant hiccups, anorexia, and a severe degree of hyponatremia (116 mEq. per liter). During the initial four days on corticotropin (25 U every six hours) there was a weight gain of 9 pounds, but starting on the fifth day there occurred a continuing diuresis from day to day culminating in a total edema weight loss of 40 pounds in 13 days.

A Physician: To say that your results in this patient were spectacular is an understatement, but how did corticotropin accomplish that feat?

Dr. Schemm: When we started using corticotropin in "hopeless" cases of congestive failure, it was our thesis that benefit might be obtained from its action on some organ-system of the body other than that concerned with sodium retention. This could possibly be in the form of improvement of the myocardium. Forgive me for talking in such vague terms for I would rather have the physiologists and endocrinologists come forth with an explanation, while we confine ourselves to the reporting of factual observations.

Be that as it may, what I really wanted to point out in this case was the fact that the diuresis induced by corticotropin was mainly a water diuresis, the total urinary sodium output from the fifth to the ninth day of its administration being only 4.3 mEq. The drop in body weight during this five-day period under consideration was 17 pounds. The plasma sodium concentration during the same period rose from 122 to 133 mEq. per liter, and finally to 142 mEq. per liter when he was discharged nine days later after having lost 40 pounds of edema weight. I want to emphasize the fact that this correction was accomplished without giving supplements of sodium salts. His eagerness to get back to his family in Canada made us relent and we gave him two doses of Thiomerin to hasten the clearing of the remaining vestige of edema during the last few days of his sojourn.

A Physician: I am fascinated by this approach to the problem of resistant edema. No doubt you are all aware that there is an increasing number of reports in the literature of cases of edematous cardiacs or nephritics who
become refractory after a while on a program which includes strict dietary sodium restriction, acidifying drugs like ammonium chloride, and intermittent doses of the mercurial diuretics. It would appear that for some of these patients at least, a new vista, a new avenue of hope has been opened by this paradoxical effect of corticotropin.

Dr. Cámara: Lest our statements lead to the promiscuous and injudicious use of corticotropin in the situation just described, especially in heart disease, I would like to make a few comments on the regimen which we ordinarily use in the management of edema and which is maintained during and after corticotropin therapy. Of course we make certain before starting that the adrenal cortices of the prospective patient will respond to the hormone; for evaluation of this, we rely rather heavily on the Thorn test. Our patients receive a neutral or acid-residue diet which contains from 9 to 30 mEq. of sodium daily, depending on the patient’s caloric intake. The emphasis is on the acid reaction of the diet residue rather than on strict sodium restriction, up to a certain point of dietary sodium intake. Ammonium chloride is administered daily in doses of 1.5 to 4 Gm.; it is given in loose powder form buffered with equal amounts of calcium carbonate in a capsule. The few patients who do not tolerate this are given the ensal form of ammonium chloride. Strict attention is paid to fluid intake which is kept between 2500 to 4000 ml. daily in the majority of cases. Daily fasting weights are obtained every morning. Our facilities at the Metabolic Unit enable us to determine daily 24-hour excretions of sodium, potassium and chloride in the urine. Those patients who do not diurese spontaneously by the fifth or sixth day and who manifest an alarming rate of weight gain are given intermittent doses of Thiomerin. A close clinical watch of the lungs in particular is kept. Adjuvant measures such as digitalis, oxygen, sedation and rest are not neglected.

I should also mention that at the outset the prospective candidate for corticotropin therapy is carefully evaluated for the presence of conditions which constitute known contraindications to the use of corticotropin, other than congestive failure.

A Physician: If such contraindications are present, then what?

Dr. Cámara: Then we are faced with a dilemma indeed, and we find our way out by carefully balancing the risks against the anticipated beneficial effects from its use. If all other measures have been tried to no avail and the patient continues to sink, then we try to pull him up by his bootstraps by using corticotropin, regardless of the contraindications. This does not mean that caution is thrown to the winds. I might briefly relate the case of F. R. to illustrate my point.

He was a 54 year old man with hypertensive heart disease who came to us within a few hours following a sudden transient episode of pulmonary edema. Following admission serious complications developed rapidly despite institution of the usual measures. Within the span of a few days he developed a pleuropericarditis (with fever and leukocytosis) followed immediately by confusion and marked agitation (possibly resulting from barbiturates and opiates used for sedation), auricular fibrillation, and then an acute dilatation of the left ventricle (as shown by serial chest roentgenograms) with the clinical picture of paroxysmal dyspnea, Cheyne-Stokes respirations of a marked degree, progressively and rapidly worsening pulmonary passive congestion, culminating in right sided failure with hepatic passive congestion and peripheral edema.

At this point we remembered our good friend corticotropin, but the following considerations made us pause for a while: (1) he had just had a recent episode of pulmonary edema, (2) he was known to have a duodenal ulcer with a flare-up only two weeks previously; (3) there was infection present (pleuropericarditis) which was being treated with antibiotics, and (4) confusion and agitation had set in. I am sure all of you will agree that each one of the above situations constituted a serious contraindication. After much deliberation, we decided to proceed with corticotropin anyway, but with the following precautions: (1) prophylactic doses of Probanthine were given regularly, (2) all stools were examined for occult blood and daily determinations of red blood cells and hemoglobin were done (blood was held in readiness all the time), (3) adequate doses of antibiotics (penicillin, streptomycin, and erythromycin) were maintained, (4) daily fluid intake of 3000 to 4000 ml. was assured by infusions of 5 per cent dextrose in distilled water, (5) mild acidification with small doses (2 Gm. daily) of ammonium chloride with the intravenous infusions was insti-
tuted and (6) we prayed as fervently as we knew how.

A profuse, spontaneous and continuing diuresis started on the third day of corticotropin administration with eventual clearing of all signs of peripheral edema and of pulmonary and hepatic passive congestion. The edema weight loss totalled 15 pounds in 10 days. To make a long story short, this patient's response to corticotropin has been the most spectacular yet that we have had in our series. A chest roentgenogram taken a week following corticotropin therapy showed that the myocardium had regained its tone, the size of the heart having returned to that prior to the onset of acute dilatation. The mild but significant degree of hyponatremia (132 mEq. per liter) was corrected (to 147 mEq. per liter), as in patient D. K., without the use of sodium salt supplements.

**Dr. Schemm:** So much now for corticotropin. We could talk for another hour about our exciting experiences with this hormone and turn the conference into a symposium on corticotropin, but, there is another facet of the problem of electrolyte deficits in cardiovascular-renal disease that I would like to touch on before we adjourn. This concerns water and electrolyte replacement in patients who develop serious gastrointestinal and surgical complications. Recognition of the need for plain water replacement besides the correction of electrolyte deficits in these patients is of paramount importance. Some of the common pitfalls include an underestimation of the water lost by vaporization through skin and lungs especially in the presence of fever and during hot weather, failure to recognize the fact that loss of gastrointestinal secretions (through vomiting, gastric suction, and diarrhea) means loss of fluid which is hypotonic with regard to sodium and therefore represents more loss of water in proportion to sodium, and failure to take into account a previously existing dehydration. Preoccupation with the electrolyte deficits often leads to underestimation of plain water needs, and administration of isotonic or hypertonic salt solutions leads to anuria and increasing azotemia. The results can be disastrous if, at this stage, the physician satisfies himself with a diagnosis of "shut down" kidneys or "post-operative nephritis" instead of attempting rehydration with plain water (5 per cent dextrose in distilled water) along with replacement of electrolyte deficits.

The case of a 58 year old housewife, R. S., is a beautiful illustration of this point. She had been hypertensive for 17 years and for 15 years had had exertional dyspnea and intermittent dependent edema. A cerebrovascular episode three years previously had caused a right-sided hemiparesis. During the last six years prior to this particular admission she had had repeated abdominal pain attributed to cholelithiasis. The day before she came in she had a sudden onset of diarrhea with frequent watery stools, generalized abdominal pain, nausea and vomiting. She waited 24 hours before seeking admission to the hospital. By that time she was acutely ill and obviously dehydrated. The blood pressure was down to 80/60 from her usual hypertensive level of 220/110. The rectal temperature was 102.4 F. and the pulse rate 100 per minute. The skin was cold and clammy. There was some cyanosis, but no dyspnea or jaundice. The fundi showed grade II hypertensive retinopathy. The tongue was dry and she complained of thirst. The heart was moderately enlarged and had a gallop rhythm. There were no abnormal lung findings. The abdomen was distended with gas-filled intestinal loops and rumbled with increased peristaltic activity. No abnormal masses could be palpated in the abdomen. Laboratory reports included a normal urine, transient leukocytosis and an electrocardiogram showing digitalis effect. A gall bladder roentgenogram showed multiple gall bladder stones. Gastrointestinal x-ray studies and intravenous urograms were negative. The clinical impression was a severe acute gastroenteritis occurring in a patient with cholelithiasis. Gastric suction was instituted and she was given intravenous fluids, antibiotics and sedatives. She got progressively worse and on the fourth day had major convulsions. The blood urea nitrogen on that day was found to be 100 mg. per 100 cc., while the plasma chloride value was at the unbelievably low level of 47.8 mEq. per liter. It was on that day that she was referred to us and was then transferred to the Metabolic Unit. The water and electrolyte balance data are extremely interesting and I would like to have them projected for you on the screen. (See table 1.)

In table 1 the intravenous fluids have been broken down into isotonic solutions (with regard to sodium and/or ammonium chloride administered) and plain water, meaning 5 per cent dextrose in distilled water. For example, 1000 ml. of 0.9 per cent sodium chloride is listed as 1000 ml. of isotonic solution, whereas 1000 ml. of 0.45 per cent sodium chloride is listed as 500 ml. of isotonic solution plus 500 ml.
of plain water, which really are its equivalent. Most of the electrolyte replacement was carried out in the form of the hypotonic (half-strength) sodium chloride solution which provided adequate amounts of water along with the needed electrolytes, as one can easily see in the Fluid Intake column.

Note during the first three days when she was on the general medical floor that both electrolyte and plain water replacement fell short of her requirements as shown by marked oliguria, rising blood urea nitrogen, high plasma specific gravity, and low plasma sodium and chloride values at the time she was transferred to the Unit. With vigorous water and electrolyte replacement, the oliguria was promptly corrected; the blood urea nitrogen rapidly returned to normal values while the electrolyte pattern was simultaneously being corrected. I want to direct your attention to the Urine column to emphasize the fact that the daily urinary excretions of sodium and chloride were small despite the copious urinary volumes from day to day. It demonstrates the “wisdom” and ability of the kidneys to conserve electrolytes when they are needed by the organism. The fact that no edema was produced by this high fluid regimen is also worth mentioning. There was in fact a weight loss of 2.6 Kg. from the fourth to the tenth day. The patient improved steadily and subsequently underwent a successful cholecystectomy.

**A Physician:** I have long wanted to see data of this sort ever since I became interested in your work, Dr. Schemm. To me they refute the oft-repeated contention that in such a situation as you described, forcing of water will result in “washing out” of the electrolytes; but do not hypotonic solutions such as 0.45 per cent sodium chloride have deleterious effects on the
red cells and the plasma solutes, particularly the proteins?

**Dr. Schemm:** I presented the same type of data at the “Salt and Water Festival” sponsored by the National Heart Institute in Atlantic City in April 1949, but I do not recall having seen the proceedings of the symposium published. You asked an interesting question with regard to hypotonic solutions which we ourselves have tried to answer by studies on patients and on ourselves. These studies were designed to see whether hypotonic solutions (0.45 per cent sodium chloride in distilled water and 2.5 per cent dextrose in distilled water) caused hemolysis of red cells and dilution of the plasma constituents. The subjects received within 28 to 70 minutes 1000 ml. volumes of these hypotonic solutions and each hour later the infusion: plasma hemoglobin, plasma specific gravity, proteins, erythrocyte count, hematocrit, hemoglobin, osmotic pressure, sodium and potassium. The same data were obtained in these subjects using isotonic solutions of sodium chloride and glucose. We found that hypotonic solutions did not cause intravascular hemolysis of red cells as judged by absence of plasma hemoglobin after their administration. Values for plasma specific gravity, osmotic pressure, proteins, erythrocyte count, hemoglobin, hematocrit and sodium showed a slight but insignificant dilution immediately after infusion, but they returned to preinfusion values an hour later. The same phenomenon was observed with isotonic solutions and curiously enough, such a dilution effect was consistently greater when isotonic saline solution was used than with hypotonic saline and either isotonic or hypotonic glucose solutions. The explanation for this may lie in the fact that isotonic saline diffuses only in the 12 odd liters of extracellular fluid, whereas the water of glucose solutions, after metabolism of the sugar, diffuses rapidly in the 50 liters of total body water, hence there is less net dilution effect on the plasma.

Our time is running short, and we have one more case that we would like to present. Go ahead, Dr. Cámara.

**Dr. Cámara:** I shall try to be brief and mention only the pertinent facts in this case.

This patient was J. S., a 68 year old housewife who came to the hospital because of gradual enlargement of the abdomen of four months' duration and anorexia. Diagnostic studies revealed the abdominal mass to be a nonfunctioning hydronephrotic left kidney with several calculi in it. Nephrectomy was delayed because of her poor clinical status, with anorexia, nausea, and vomiting. Gastric suction was instituted on the twelfth hospital day and continued through the seventeenth day. The amount of gastric suction totaled 5,460 ml. during those six days when no electrolyte replacement whatsoever was given. She grew progressively weaker and apathetic and in the evening of the seventeenth hospital day she went into deep coma following convulsions. She was in this state when she was transferred to the Metabolic Unit on the eighteenth day. A presentation of the water and electrolyte data on her will show her progress more vividly than words can describe. (See table 2.)

Of particular interest in this table of data are the extreme degree of hyponatremia and hypochloremia that existed when we first saw her. This severe chemical imbalance undoubtedly was responsible for the coma, for following the first two infusions consisting of 1000 ml. of 0.45 per cent sodium chloride (with 2 Gm. of ammonium chloride and 2 Gm. of potassium chloride) and 1000 ml. of 0.9 per cent sodium chloride, she roused from her deep coma and started to respond. The following day after more electrolyte replacement she was sitting up in bed reading her get-well cards.

The intravenous fluids administered to this patient were partitioned into isotonic solutions and plain water, isotonicity being calculated on the basis of sodium chloride and ammonium chloride content of the fluids administered, as in the case of the data on the preceding patient. In other words, 1000 ml. of 0.9 per cent sodium chloride was listed as 1000 ml. of isotonic solution (as was 1000 ml. of solution containing 0.45 per cent ammonium chloride), whereas 1000 ml. of 0.45 per cent sodium chloride was considered to be 500 ml. of isotonic solution and 500 ml. plain water. Except for two liters on the eighteenth day and one liter on the twentieth day, of 0.9 per cent sodium chloride, all the sodium replacement in this patient was carried out with 0.45 per cent sodium chloride.
### Table 2.—Fluid and Electrolyte Data on Patient J. S., 68, F.

<table>
<thead>
<tr>
<th>Hospital Day</th>
<th>Surgical Floor</th>
<th>Metabolic Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12 13 14 15 16 17</td>
<td>18 19 20 21 22 23</td>
</tr>
<tr>
<td>Fluid intake, ml.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1) Oral</td>
<td>100 0 290 600 0 110</td>
<td>0 430 2140 1330 2370 2090</td>
</tr>
<tr>
<td>(2) I.V.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Isotonic</td>
<td>0 0 0 0 0 0</td>
<td>4000 2000 1500 0 500 0</td>
</tr>
<tr>
<td>(b) Plain H₂O</td>
<td>3000 4300 3000 4500 4500 6000</td>
<td>0 2000 500 2000 1500 2000</td>
</tr>
<tr>
<td>(3) Total</td>
<td>3100 4300 3290 5100 4500 6110</td>
<td>4000 4430 4140 3330 4370 4030</td>
</tr>
<tr>
<td>Body wt., Kg.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>71.2 70.5 68.4 67.5 66.8 66.4</td>
</tr>
<tr>
<td>Urine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1) Volume, ml.</td>
<td>1200 2650 3200 2520 2500 3200</td>
<td>4830 4240 3250 3100 3490 2970</td>
</tr>
<tr>
<td>(2) Sodium, mEq.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(3) Chloride, mEq.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(4) Potassium, mEq.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric suction volume, ml.</td>
<td>1900 900 520 600 940 600</td>
<td>0 0 0 0 0 0</td>
</tr>
<tr>
<td>Electrolyte replacement in I.V.'s</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1) Sodium, mEq.</td>
<td>0 0 0 0 0 0</td>
<td>462 308 231 0 77 0</td>
</tr>
<tr>
<td>(2) Chloride, mEq.</td>
<td>0 0 0 0 0 0</td>
<td>410 388 244 13 131 0</td>
</tr>
<tr>
<td>(3) Potassium, mEq.</td>
<td>0 0 0 0 0 0</td>
<td>107 80 13 13 54 0</td>
</tr>
<tr>
<td>Plasma values</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1) Sodium, mEq./L.</td>
<td></td>
<td>103</td>
</tr>
<tr>
<td>(2) Chloride, mEq./L.</td>
<td></td>
<td>57.4</td>
</tr>
<tr>
<td>(3) Potassium, mEq./L.</td>
<td></td>
<td>2.7</td>
</tr>
<tr>
<td>(4) CO₂C.P., mEq./L.</td>
<td></td>
<td>31.0</td>
</tr>
<tr>
<td>(5) Sp. gravity</td>
<td></td>
<td>1.0214</td>
</tr>
<tr>
<td>(6) Osm. pressure</td>
<td></td>
<td>1.0214</td>
</tr>
<tr>
<td>(mOsm./L.)</td>
<td></td>
<td>103</td>
</tr>
<tr>
<td>Blood urea N, mg.%</td>
<td></td>
<td>14</td>
</tr>
</tbody>
</table>

Note that the initial plasma specific gravity on the day she came to the Unit (eighteenth hospital day) was low, and despite the use of hypotonic (half-strength) sodium chloride solutions, the remaining functioning kidney was able to effect correction of concentration, correction of pattern, and correction of volume of the extracellular fluid (rapid weight loss of 4.8 Kg. in five days). As soon as she was gotten into optimal condition a few days later, a successful nephrectomy was done.

**Dr. Schemm:** We have had our best results results in correcting hyponatremia and/or hypochloremia by giving a sufficient amount of electrolytes and at the same time an adequate amount of plain water, as these two cases demonstrate. We have not seen the extra plain water interfere with correction of pattern or induce signs or symptoms of so-called water intoxication.

When we have used hypertonic (2 or 3 per cent) sodium chloride solutions we have found them sometimes rapidly effective only in improving pattern defects, but disadvantageous as compared to isotonic, or even hypotonic solutions, in that the hypertonic solutions do not allow for correction of the usually coincident and more important plain water deficits. In our experience, hyponatremia does not always indicate dilution of the extracellular fluid because, paradoxically enough, we have seen hyponatremia coexist with a high specific grav-
ity of the plasma, and we have seen it corrected by the use of hypotonic solutions (with regard to sodium) with coincident return of plasma specific gravity to normal values.

**Summary**

In this discussion of some of the points that have interested us in the correction of electrolyte deficits in cardiovascular-renal disease, we briefly reviewed the salt-losing syndrome in terminal nephritics and in hypertensives with advanced renal damage, and incidentally delved into the concepts of edema formation as we discussed its opposite mechanism. We found ourselves drawn into a discussion of potassium metabolism in the process, touching on the subject of “potassium losers.” Next in the panorama of this multifaceted problem came the management of edematous patients who developed hyponatremia on the diuretic regimen (without losing their edema) or who became mercurial fast in “midstream”; i.e., after losing about half their edema. Under such dire circumstances, we showed how sodium chloride might be used to good advantage.

The promising use of corticotropin (ACTH) in hopelessly resistant cases of cardiac edema or in near-terminal severe cases of myocardial insufficiency, with incidental correction of a coexisting hyponatremia (accomplished without the use of sodium supplements) was described. Finally, we discussed in detail our use mainly of hypotonic solutions of sodium salts in correcting concentration as well as pattern and volume disturbances of the extracellular fluid in cardiovascular-renal patients who develop serious gastrointestinal and surgical complications. We emphasized that in such patients we have obtained the best end results with mainly hypotonic and isotonic, rather than hypertonic salt solutions. With this form of electrolyte replacement therapy, we have seen more floating on water and less drowning in brine!
The Correction of Electrolyte Deficits in Cardiovascular-Renal Disease

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