THE EFFECTS OF ACUTE HYPOCHLOREMIA ON THE DISTRIBUTION OF BODY FLUID AND COMPOSITION OF TISSUE ELECTROLYTES IN MAN*

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INTRODUCTION

IN THE COURSE of investigating metabolic alterations associated with the withdrawal of gastric contents in man, it soon became apparent that the composition of the gastric juice markedly influences the induced response.[46] Thus the withdrawal of gastric juice with a high free acid, *i.e.*, a high preponderance of chloride over sodium content of the gastric secretions, would induce a sequence of metabolic changes different from patients with so-called anacidity, wherein the chloride content may be almost equivalent to the sodium content of the gastric aspirate.[44]

This study investigates those alterations in fluid and electrolyte balance in patients with a high free acid content of their gastric secretions. The withdrawal of chloride in excess of sodium is responsible for a number of electrolyte shifts. Some of these metabolic changes and the therapeutic repair solutions indicated for their correction are described. Attention is focused upon the alterations in the quantity and distribution of body water, changes of tissue electrolytes as determined by analysis of muscle biopsies, and their clinical significance.

PROCEDURE

Five patients admitted to the hospital as candidates for surgical intervention were rendered hypochloremic by the continuous withdrawal of gastric contents through an indwelling gastric tube attached to gastric suction. In the first two patients, gastric secretion was stimulated by the subcutaneous injection of 0.5 mg. of histamine three times per day. In the three other patients, gastric secretion was stimulated by the oral ingestion of 30 ml. of 7 per cent ethyl alcohol every four hours during waking hours. These patients were chosen because they all presented a high free acid content of their gastric secretions. Each patient willingly cooperated in this investigation.

During this period they were permitted to eat a salt-free diet, with the gastric tube clamped for one hour after each meal. Each patient was given a large amount of fluid intravenously as 5 per cent dextrose in distilled water, varying from three to five liters per day.

As the patients developed hypochloremia, they generally suffered from lethargy, anorexia, nausea, increased irritability, and at times abdominal pain. At the completion of the experiment the patients were given from 13.5 Gm. to 27 Gm. of sodium chloride as normal saline solution intravenously each day until the serum chlorides were normal. This was accomplished usually in one to three days.

The following determinations were performed: (1) serum electrolytes, (2) sodium, chloride, and potassium content of the aspirated gastric juice, (3) alterations produced by hypochloremia upon urinary chloride, sodium, and potassium content, (4)

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TABLE I. *The Content of Chloride, Sodium and Potassium of the Fluid Withdrawn by Gastric Aspiration.*

Patient Diagnosis	Quantity of Gastric Fluid Aspirated. 1.	Number of days of Withdrawal	Chloride mEq/1.	Chloride Total Amount Aspirated (mEq.)	Sodium mEq/1.	Sodium Total Amount Aspirated (mEq.)	Potassium mEq/1.	Potassium Total Amount Aspirated (mEq.)
1. G. W. Inguinal Hernia	2.4	6	92	225	20	49	10	24
2. L. S. Cholecystitis	8.4	4	102	857	50	429	11	92
3. V. C. Carcinoma of Rectum	8.3	9	73	606	40	332	8	66
4. L. G. Duodenal Ulcer	9.3	6	110	1023	42	391	8	74
5. J. C. Duodenal Ulcer	4.8	3	90	432	33	158	4	20

alterations produced in total body water, interstitial water, and plasma volume, and (5) changes produced in the water and electrolytes of striated muscle.

CHEMICAL METHODS AND CALCULATIONS

Serum chloride was performed by the technic of Schales and Schales.[60] Serum protein concentrations were determined by the method of Weichselbaum,[66] serum urine and gastric sodium and potassium by an internally compensated Perkin-Elmer flame photometer, and the hematocrit as described by Musser and Wintrobe.[53] The carbon dioxide-combining capacity was determined by the gasometric method of Van Slyke and Cullen.[58] Urine chloride concentrations were ascertained by the modified Volhard-Harvey titration method. Plasma volume and thiocyanate (available fluid) space were measured by the procedure developed by Gregersen and Stewart, adapted for the Evelyn colorimeter.[36]

Total body water was determined by deuterium dilution and analyzed by the mass spectrograph. The blood sample obtained after the administration of 25 Gm. of deuterium oxide was vacuum distilled to evaporate the water, which was placed in an equilibrium tube with a catalyst (platinum oxide) and was frozen in an alcohol-dry ice bath. The air above the water and catalyst was removed by a vacuum pump and this air was replaced by hydrogen gas after which the equilibrium tube was sealed and allowed to stand overnight. During this period the hydrogen gas and the hydrogen atoms of the water would exchange. After equilibrium had occurred, the hydrogen gas was analyzed by the mass spectrograph for the deuterium content. (The author is indebted to Dr. Alfred Nier for these determinations.)

METHODS OF CHEMICAL ANALYSIS OF MUSCLE BIOPSIES

Muscle biopsies averaging 2 Gm. were obtained from either the deltoid or gastrocnemius muscle. The opposite muscle was usually analyzed when several biopsies were taken from the same patient during different electrolytic states. One muscle sample was analyzed at the beginning of the experiment, and another after the crystalloid defect had been produced. Analysis of a large number of muscle biopsies of patients on surgical wards, during the preoperative state and in apparently normal electrolyte balance, presented such a great dispersion that it was considered inadvisable to develop an average normal for water and electrolytes. It was accordingly considered advisable to study different states in the same patient, the patient thereby being his own control. Anesthesia was obtained by infiltrating the skin and subcutaneous tissue with 1 per cent procaine at a significant distance from the site where the muscle was to be obtained.

TABLE II. *Alterations in Serum Concentration of Hemoglobin, Protein, and Electrolytes, Induced by Withdrawing Gastric Contents.*

Case No.		Hemoglobin gm. %	Hematocrit %	Protein gm. %	Blood Urea Nitrogen mg. %	Chloride mEq/1.	CO_2 Combining power mEq/1.	Sodium mEq/1.	Potassium mEq/1.
	Normal	15.5	47	7.6	—	109	24	146	5.2
1	After Aspiration	15.0	45	7.7	—	86	36	148	4.0
	Normal	13.1	43	7.6	—	95	21	153	4.0
2	After Aspiration	8.9	32	7.0	9.0	80	31	131	5.3
	Normal	12.6	46.5	5.3	11	105	21	143	3.4
3	After Aspiration	13.4	46.5	6.9	8	72	↑38	127	2.5
	Normal	15.0	45.2	6.0	16	101	26	145	5.0
4	After Aspiration	14.8	42.0	7.7	24	80	↑38	130	3.5
	Normal	15.5	46.5	6.5	8	96	22	140	4.8
5	After Aspiration	15.0	47.0	6.8	12	72	↑38	145	3.9

An incision through the skin was painless, but some pain was experienced when the actual muscle was severed and a portion excised. By working rapidly, the biopsy could be obtained with a minimum of discomfort to the patient.

The muscle biopsy was quickly blotted with dry gauze. The fresh tissue was freed of visible fat and some connective tissues with a scissors and placed in a tared weighing bottle. The water content was determined by drying the tissues overnight in an electric oven at 105° C. Fat was determined by extracting the tissue with ethyl ether and petroleum ether, according to the method of Hastings and Eichelberger.[38] The dry tissue was then divided into two parts, and the chloride content was determined on one aliquot after boiling with concentrated nitric acid in the presence of an excess of silver nitrate, and analyzed by the Volhard titration technic. The sodium and potassium contents were determined by means of an internally compensated flame photometer on the other portion of tissue, which was ashed overnight in a platinum crucible in an oven at 450° C.

All values are presented in terms of fat-free weight, since it has been determined that fat is deposited dry. Accordingly, all muscle analysis must be presented on the basis of fat-free weight because the addition of this variable produces results which are not comparable. Analyses have been done on over 100 specimens of muscle, with the following deviations from the mean:

Water ..... ±0.1 per cent
Chloride ..... ±2.3 per cent
Sodium ..... ±1.8 per cent
Potassium ..... ±1.9 per cent

Electrolyte concentration of extracellular fluid as mEq. per Kg. of water was calculated by the method described by Yannet and Darrow.[67]

$$\frac{[Cl]_{ser}}{[H_2O]_{ser} \times 0.95} = [Cl]_e$$

$$\frac{[Na]_{ser} \times 0.95}{[H_2O]_{ser}} = [Na]_e$$

$$[K]_e = [K]_{ser}$$

Muscle per 100 Gm. fat-free solids (FFS):

$$(H_2O)_e \text{ in grams} = \frac{(Cl - 1)}{[Cl]_e}$$

$$(Na)_e \text{ in mM.} = (H_2O)_e \times [Na]_e$$

$$(Na)_i \text{ in mM.} = (Na) - (Na)_e$$

Subscripts "ser", "e", and "i" refer to serum, extracellular and intracellular phases respectively.
[ ] refers to concentration.
( ) refers to total amount expressed in mM., mEq., or Gm

RESULTS

The data are summarized in Tables I to VI, and can best be presented by analyzing the various component parts of this study.

THE QUANTITY AND CONTENT OF CHLORIDE, SODIUM, AND POTASSIUM OF THE GASTRIC ASPIRATE

Table I presents the quantity and content of gastric juice withdrawn. The quantity withdrawn varies from 2.4 liters in Case 1, to 9.3 liters of gastric juice in Case 4. No significant features could be established that influenced the composition of gastric juice. Even when the patients had been rendered hypochloremic, there was no diminution of chloride in the gastric aspirate.

The chloride content of the gastric fluid varied from 73 to 110 mEq. per liter, and averaged 93 mEq. per liter. The total quantity of chloride withdrawn in the aspirate fluctuated from 225 mEq. to 1023 mEq., and averaged 629 mEq.

In contrast to these high values are the lower figures for the sodium content of the gastric juice. This varied from 20 mEq. per liter to 50 mEq. per liter, and averaged 37 mEq. per liter, or approximately one-third that of the chloride content. The total quantity of sodium aspirated varied from 49 mEq. to 429 mEq., and averaged 272 mEq.

The potassium content was significant, and fluctuated from 4 mEq. per liter to 11 mEq. per liter. The average total quantity of potassium aspirated in the gastric content was 55 mEq.[44]

THE ALTERATIONS OF THE SERUM CONCENTRATIONS OF CERTAIN CONSTITUENTS INDUCED BY WITHDRAWING GASTRIC CONTENT

The alterations of serum concentrations of hemoglobin, protein, urea nitrogen and electrolytes are presented in Table II.

The change in hemoglobin value was slight in most cases except in Case 2, where there was a significant drop. The reason for this is not apparent. Hematocrit decreased somewhat in all but one instance. The serum protein also fluctuated in a variable manner, increasing in content in some individuals and decreasing in others. The reason for this is not clear. The blood urea nitrogen increased in certain patients and, as has been demonstrated previously, there is a diminution in renal function during induced hypochloremia.[6] The increase in blood urea nitrogen may be a reflection of this alteration.

The most significant changes occurred in the serum electrolytes, with a sharp drop in the serum chloride in all patients. It is of interest that in a short period of three days of constant gastric suction, the chloride content of the serum in Case 5 dropped from the normal level of 96 mEq. per liter to the low level of 72 mEq. per liter. The average drop in serum chloride was 23 mEq. per liter. This demonstrates the rapidity with which hypochloremia can be induced by gastric suction.[42]

A concomitant rise in the carbon dioxide combining power occurred. In the institution where these studies were performed, the highest recorded carbon dioxide combining power is 38 mEq. per liter, and any value above this is merely indicated as being higher than 38 mEq. per liter. In three patients on this rather short regimen of gastric aspiration, the high carbon dioxide combining power of over 38 mEq. per liter was induced.

The serum sodium content fluctuated. The value dropped significantly in three patients, the decrement varying from 15 to 22 mEq. per liter. There was a slight increase in serum sodium concentration in two patients, which might reflect an alteration in concentration due to changes in hydration, rather than absolute increase in plasma sodium.

The potassium content of the serum decreased in four of the five patients, the decrement varying from 0.9 to 1.5 mEq. per liter. One patient (Case 2) manifested an increased potassium level of 1.3 mEq. per liter.

THE URINARY SECRETION OF ELECTROLYTES DURING THE WITHDRAWAL OF GASTRIC CONTENT (TABLE III)

The various urinary values are presented according to that excreted during the first

TABLE III. *Urinary Excretion of Electrolytes During the Withdrawal of Gastric Contents.*

Patient	Urine Volume	Chloride		Sodium		Potassium	
	1.	mEq/1	Total Excreted (mEq)	mEq/1	Total Excreted (mEq)	mEq/1	Total Excreted (mEq)
1. *Average:*							
1st half of experiment (3 days)...	8.2	4.4	36.1	3.0	24.6	4.3	35
2nd half of experiment (3 days)..	7.7	0.8	6.2	5.2	38	6.5	50
2. *Average:*							
1st half of experiment (2 days)...	2.0	3.5	7.0	4.0	8.0	3	6.0
2nd half of experiment (2 days)..	6.2	0.3	1.9	7.2	44.6	5	31.0
3. *Average:*							
1st half of experiment (5 days)...	15.5	1.0	15.5	2.1	32.5	2.0	31.0
2nd half of experiment (5 days)..	14.8	0.2	3.0	6.4	94.7	8.2	121.4
4. *Average:*							
1st half of experiment (3 days)...	8.7	2.5	21.7	3.0	26.1	4.2	36.5
2nd half of experiment (3 days)..	6.7	0.5	3.3	8.2	54.9	10.9	73.2
5. *Average:*							
1st half of experiment (2 days)...	4.1	3.0	12.3	2.5	10.2	4.5	18.4
2nd half of experiment (2 days)..	15.5	1.0	5.5	6.0	33.0	20.0	110.0

half of the experiment, and that excreted during the second half, to note if a direction of shift of urinary electrolytes can be detected as the effects of withdrawal of gastric juice continues.

The *chloride* content of the urine fluctuated markedly between the first and second parts of the experiment. The average chloride excreted during the first portion of the experiment was 18.3 mEq., and varied from 7.0 mEq. to 36.1 mEq. In contrast, during the latter period of gastric aspiration the average chloride excreted by the five patients was 4.0 mEq., and fluctuated from 1.9 to 6.2 mEq. A marked diminution in the excretion of this ion is demonstrated as the period of gastric secretion continues.

An opposite effect was noted in the *sodium* excretory pattern. The quantity excreted during the first half of the experiment is more or less equal to the quantity of chloride excreted, and averaged 21 mEq. During the second half of the experiment, however, there was a sharp increase in the sodium content of the urine. The average quantity excreted was 53 mEq., and varied from 13.4 mEq. to 62.2 mEq.

The *potassium* excreted in the urine more or less paralleled the sodium excretory pattern, in which there was a marked increase in the quantity of potassium excreted during the second half of the experiment from that excreted during the first half. Thus, during the first days of gastric aspiration an average of 25 mEq. of potassium was excreted, and during the second half of the experiment an average of 77 mEq. of potassium was excreted in the urine. In certain patients, large quantities of potassium were excreted; thus Case 5 excreted 110 mEq. of potassium during the two-day period of the experiment.

THE EFFECTS OF WITHDRAWING GASTRIC CONTENTS UPON THE BODY WEIGHT, TOTAL BODY WATER, AND CORPOREAL DISTRIBUTION OF WATER

The effects of withdrawing gastric content and concurrently administering large quanties of 5 per cent dextrose in distilled water intravenously upon the body weight, total body water, plasma volume, and the interstitial volume are presented in Table IV.

Weight and Total Body Water Alterations. It will be noted that there was a significant drop in the weight of these patients, the average decrease being 3.7 Kg. Fluids were rapidly lost (both by gastric aspiration and urination), with a resultant loss of total

body water as reflected by measurements of body water by the deuterium dilution technic. It was possible to do these determinations in three patients, and an average decrease of total body water equal to 2.7 liters was demonstrated.[35]

Plasma and Extracellular Volume Alterations. In an effort to ascertain the particular body phase from which the water was lost, an estimation of the plasma volume and the interstitial volume was made. An average decrease of plasma volume equivalent to 0.36 liters and a decrease in the interstitial space equal to 1.7 liters was observed. Thus, an average of 2.1 liters were lost from the extracellular space (plasma and interstitial space) and a smaller quantity (0.6 liters) probably lost from the intracellular compartment.

THE ALTERATIONS INDUCED BY WITHDRAWAL OF GASTRIC CONTENT: UPON MUSCLE ELECTROLYTES AND WATER

Tissue alterations induced by the withdrawal of gastric secretions were studied in the five patients. A sample of muscle was analyzed before and after hypochloremia was induced (Tables V and VI). An average loss of water equal to 23 ml. per Kg. of muscle occurred. Muscle water in all patients diminished. A diminution of chloride in the muscle of each of the patients was noted, with the average decrease being 8 mEq. per Kg. of fat-free tissue. Associated with the decrease of the chloride content was an average increase of 14 mEq. per Kg. in the sodium content of the tissue. A decrease in the potassium content of the tissue occurred in each of the patients, and averaged 17 mEq. per Kg. of fat-free tissue. The quantity of potassium lost fluctuated from 8.4 mEq. to 33.1 mEq. per Kg. of fat-free tissue.

In order to rule out influences due to alterations of hydration which would affect measurements of the muscle electrolyte content, the concentrations of chloride, sodium and potassium per 100 Gm. of *fat-free solids* were determined, and are presented in Table VI. Since the muscle solids remained nearly constant during the short periods of these experiments and are not affected by alterations of the extracellular phase, expressions of muscle electrolytes in terms of fat-free solids will present the absolute electrolytic changes occurring in the different situations.

A decrease in the *chloride* content of muscle occurred in each instance, averaging a net decrease of 4.9 mEq. per 100 Gm. of fat-free solids.

A gain of the muscle *sodium* occurred, averaging 4.3 mEq. per 100 Gm. of fat-free solids, and varying from 2.2 mEq. to 7.6 mEq.

There was an average loss of 11.1 mEq. of *potassium*, with a rather wide variation among the different patients. The smallest potassium loss was manifested by Case 4, whose loss was 6.5 mEq. per 100 Gm. of solids, and the greatest loss occurred in Case 5, whose potassium depletion per 100 Gm. of fat-free solids equalled 18.7 mEq. These data demonstrate an absolute loss of tissue chloride and, to a much greater extent, tissue potassium. This is rather surprising, since the primary solution being withdrawn from the patient (gastric secretion) contains chloride in great excess over potassium.

The distribution of the electrolytes within the muscle, *i.e.*, between the intra- and extracellular positions, is permitted by utilizing the premise that practically all tissue chloride is situated extracellularly (Table VI). The extracellular content of the chloride decreased in each patient studied. The extracellular water content of the muscle decreased an average of 24.4 Gm. per 100 Gm. of fat-free solids, and varied from 17 to 34 Gm. It is of interest that the average intracellular water decrement was 23 Gm. per 100 Gm. of fat-free solids. The tremendous variation shown in these patients demonstrates the unreliability of average values. Furthermore, there was no correlation be-

tween the extra- and intracellular water content of the tissues. Thus, Case 2 lost a large amount of extracellular water, 34 Gm. per 100 Gm. of fat-free solids, and 16 Gm. of intracellular water. Contrariwise, a much greater quantity of intracellular water was lost by Case 3 than the extracellular water decrement. The explanation for these divergent exchanges is not clear. This behavior of tissue water exemplifies the wisdom of expressing alterations of tissue electrolytes on the basis of the solid content of the tissue.[20]

The essential sodium changes consisted of an extracellular decrement, averaging 4.4 mEq. per 100 Gm. of fat-free solids, and a rather large increment of the intracellular sodium which averaged 8.4 mEq. per 100 Gm. of fat-free solids and fluctuated from 5.8 to 11.2 mEq. per 100 Gm. fat-free solids. There was no correlation between the quantity of extracellular sodium lost and that gained intracellularly.

Alterations in the intracellular sodium and potassium concentrations expressed as mEq. of intracellular sodium and potassium per Kg. of water show an average gain of 36 mEq. of intracellular sodium and an average loss of 31.8 mEq. of potassium per Kg. of water.

DISCUSSION

The data of this investigation reveal that the withdrawal of gastric juice from humans sets off a chain reaction of metabolic alterations which affect the entire fluid and electrolytic structure of the organism. For purposes of discussion the observed effects will be presented under two headings:

I. ALTERATIONS INCIDENT TO THE LOSS OF TOTAL BODY ELECTROLYTES

Chloride, and to a lesser extent sodium and potassium, are lost from the aspirated gastric juice. Sodium and potassium are excreted in significant quantities by the kidneys as the period of gastric aspiration progresses. There is, then, a net loss of body crystalloids. In these experiments an attempt was made to avoid the factor of dehydration by administering to each patient ionic-free fluid intravenously in excess of that siphoned out of the stomach. The attempt was unsuccessful and dehydration developed because of the body's inability to retain the administered water which was rapidly excreted.[29, 42, 48, 49] This dehydration is manifested by the loss of weight in each patient, a loss of body water as measured by deuterium dilution, a loss of tissue water as exemplified by analysis of the water content of muscle.

II. ALTERATIONS INCIDENT TO THE REMOVAL OF AN EXCESS OF CHLORIDE OVER SODIUM

Serum alterations associated with this defect consist of the well-known hypochloremia and alkalosis. There is a concomitant decrease in the serum sodium concentration and a slight decrease in the potassium content of the serum in most patients.[18, 34, 40]

Indices showing the direction and magnitude of the electrolyte changes are offered by analyzing muscle for its total water and electrolyte content and calculating the distribution of the water and electrolytes between the intra- and extracellular phases. Such studies have been performed intensively in animals, and have yielded valuable data for understanding the electrolyte balance in different states. Such studies in humans have been meager because of certain inherent annoyances of the technic.[4, 5, 51] Because of the possibility of specie differences it is essential that such analyses be performed in the human. In this study the patient acted as his own control, and muscle segments were analyzed before and after the electrolyte defect had been produced.

Four significant alterations were observed in the muscles after hypochloremia had been established. These were (1) a loss of muscle water, (2) a decrease of muscle chloride, (3) a decrease of muscle potassium, and (4) a significant increase of muscle sodium. By

TABLE IV. *Effects of Withdrawing Gastric Contents Upon Body Weight, Total Body Water, Plasma Volume and Interstitial Volume.*

Patient Number	Weight (kg)			Total Body Water (l.)			Plasma Volume (l.)			Interstitial Space (l.)		
	Normal	Hypochloremia	Balance	Normal	Hypochloremia	Balance	Normal	Hypochloremia	Balance	Normal	Hypochloremia	Balance
1.	66	62.7	−3.3	39.6	36.6	−3.0	3.1	2.6	−0.5	9.7	6.6	−3.1
2.	51	47.7	−3.4	30.9	28.1	−2.8	2.6	2.4	−0.2	8.2	7.2	−1.0
3.	51.6	45.0	−6.6	—	—	—	3.0	2.4	−0.6	10.2	7.8	−2.4
4.	62.5	59.3	−3.2	40.0	37.8	−2.2	3.5	3.0	−0.3	10.5	9.2	−1.3
5.	68	66	−2.0	—	—	—	3.2	3.0	−0.2	9.5	8.7	−0.8

utilizing the premise that practically all of the chloride is in the extracellular space, one can compute the distribution of sodium, potassium, and water between the intracellular and extracellular compartments. An understanding of this distribution is of great importance in devising repair solutions. If a defect is exclusively extracellular, it is necessary only to administer the proper repair solution to correct the extracellular defect. Since all repair substances are introduced into the extracellular space (hypodermoclysis, venoclysis, or ingestion), it is essential in the presence of intracellular defects that the repair substances deposited outside the cell boundary will evoke the necessary alterations to correct the intracellular defect.

The utilization of the concept of the extracellular position of the chloride ion might be challenged. Recent studies by Deane, *et al.*,[22] have shown that a significant quantity of chloride is intracellular. Overman[56, 57] has demonstrated a breakdown of the selective cell membrane permeability during malaria, and the author has shown the same phenomenon to occur after anoxia and hypotension.[4] However, careful analyses of tissues of normal animals by Manery and Hastings[45] and others have shown that chloride exists in most tissues in the same concentration as an ultra-filtrate of plasma.[32, 38, 47, 63] It may thus be assumed that most chloride is extracellularly positioned, and since there is nothing in these experiments, such as severe fever or anoxia, to disrupt the normal selective permeability functions of the cell membranes, it would appear safe to adhere to the concept of the extracellular position of chloride for these calculations. Even should this concept not be entirely correct, the introduced error would merely be one of magnitude rather than direction of the calculated alterations.

The significant electrolytic tissue alterations consisted of a rather marked ingress of sodium into the intracellular position and an egress of potassium out of the cell. These changes are the same as described for animals under similar conditions,[19, 21] and are similar to those hypothecated by Elkinton, *et al.*,[28, 29, 31] for patients by balance technics. The mechanism whereby withdrawal of chloride (an extracellular ion) produces an exodus of potassium from the cell and an ingress of sodium into the cell is not completely understood although various theories have been promulgated. Darrow[19, 21] believes that the carbon dioxide combining power exerts a regulatory role in determining the cationic placement. In recent studies by Cooke, *et al.*,[12, 13, 14] it was shown that the high carbon dioxide combining power associated with respiratory acidosis did not produce significant alterations in the muscle electrolytes. This is in sharp contrast to the muscle alterations produced by metabolic alkalosis in which the high carbon dioxide combining power is associated with profound alterations of the tissue electrolytes. Cooke, *et al.*, accordingly hypothecate that the fundamental factor which induces the intracellular alterations is change of pH of

the extracellular space. The fact that in potassium deficiency with alkalosis, the increased intracellular sodium usually equals two-thirds the intracellular potassium decrement is interpreted to indicate that the hydrogen ion within the cell is exchanged for potassium of the extracellular fluid when potassium salts are given. Thus, in potassium deficiency *per se* an intracellular acidosis apparently accompanies the extracellular alkalosis. Whereas Cooke explains this phenomenon on the basis of alterations in answer to osmotic demands and effected by the mass action law, Elkinton, *et al.*, hypothecate that cation exchanges across the cell boundary are related to metabolic activities of the cell and the expenditure of energy rather than to passive transfers resulting from differential permeabilities.[29]

KIDNEY DYSFUNCTION IN HYPOCHLOREMIA

Because renal function is essential for the maintenance of proper extracellular composition, which in turn governs the intracellular electrolyte content, it becomes essential to examine the excretory partition of electrolytes during acute hypochloremia and to note the effects of the crystalloid imbalance upon renal function.

URINARY CRYSTALLOID CONTENT DURING HYPOCHLOREMIA

Three distinct electrolyte excretion patterns are observed (Table IV). The data are presented by analyzing the excretion patterns during the first half of the experiment, and comparing them with those during the second half of the experiment. It would have been preferable to have performed daily determinations which would have offered a running profile of the alterations. This was not possible for technical reasons, and the data obtained by pooling the specimens of the first half of the period of gastric aspiration and comparing them with excretion pattern of electrolytes during the second period emphasize the alterations that occurred as the withdrawal of gastric juice continued. The three noteworthy observations were: (1) whereas chloride was excreted in significant quantities in the beginning of the experiment, the urinary chloride content diminished precipitously during the second period; (2) sodium was excreted in significant quantities and more or less paralleled the quantity of chloride excreted in the beginning of the gastric withdrawal regimen; during the second half there was a marked increase in the amount of sodium excreted; (3) urinary potassium increased markedly as the regimen of gastric withdrawal continued.

TABLE V. *Muscle Composition of Electrolytes as Altered by Acute Hypochloremia—mEq/kg. of Fat-Free Tissue.*

Patient	Diagnosis	Muscle Water ml/kg.	Chloride	Sodium	Potassium
1	Normal.....	790	28.5	39.5	80.4
	Hypochloremia...	762	20.0	50.0	72.0
2	Normal.....	800	29.4	38.0	84.5
	Hypochloremia...	778	21.2	47.4	70.4
3	Normal.....	785	27.6	42.0	83.0
	Hypochloremia...	750	19.5	56.5	68.7
4	Normal.....	770	25.7	37.4	79.0
	Hypochloremia...	765	17.6	52.5	65.4
5	Normal.....	795	27.8	36.5	85.5
	Hypochloremia...	772	19.0	58.0	52.4

These observations on urinary electrolytes can be readily interpreted in terms of the observed plasma and tissue electrolyte changes. Diminished chloride excretion is an attempt to conserve an ion which is being wasted from another route. The increased urinary sodium probably reflects the body's mechanism to rid itself of the cation not completely combined with bicarbonate. The excretion of potassium by the kidneys is an obligatory process subsequent to the exit of the ion from the cell.[52]

In view of the paramount importance of kidney function in controlling the crystalloid composition of the organism, it appears surprising that the defects induced by withdrawing corporeal chloride result in damage to kidney function.[6]

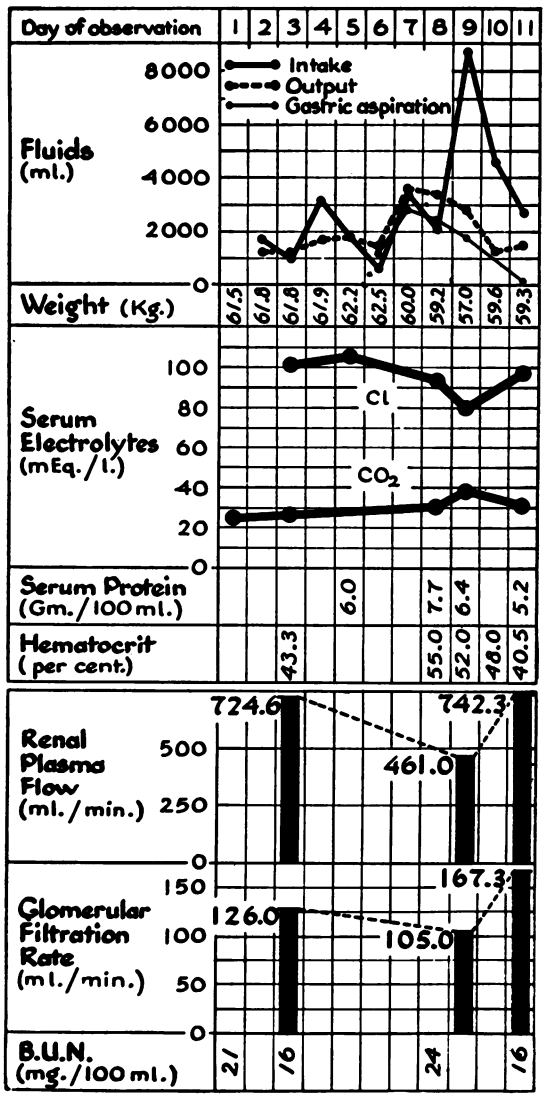

FIG. 1. Demonstration of the effects of gastric aspiration on serum chloride and carbon dioxide combining power in Case 4. The diminution in renal plasma flow and glomerular filtration rate when hypochloremia has been induced is evident. When the electrolyte status has been corrected, kidney clearance returns to normal. (Ariel and Miller,[6] reproduced from *Surgery,* with permission of C. V. Mosby Co.)

A decreased serum chloride evokes an increased blood urea nitrogen. The mechanism has been commented upon, but remains enigmatic.

Figure 1 presents the results of gastric aspiration upon renal function in Case 4, and shows the marked diminution in renal plasma flow and glomerular filtration rate resulting from the induced hypochloremic alkalosis. The rapid return of the kidney clearances to normal levels after the hypochloremia was corrected by the administration of 27 Gm. of sodium chloride in two days is evident.

SHIFTS OF BODY WATER DURING HYPOCHLOREMIA

Alterations in the fluid balance of the individual induced by the withdrawal of gastric juice were profound. The patients persistently lost weight,[35] due essentially to loss of total body water from each compartment. Analysis of the muscle biopsies for total water and the distribution of the water revealed a loss of total muscle water, the loss being contributed by both the extra- and intracellular compartments. This finding is at variance with observations by others on animals under similar conditions. When Darrow tied off the pylorus of rats and permitted adequate fluid, a high intracellular water developed, and the muscle potassium and intracellular sodium remained normal.[21] He attributes the high intracellular water to the low concentration of the serum sodium. The duration of Darrow's experiment was a little over one day, which may be a factor in the different fluid changes from those observed here. The observation by Elkinton, *et al.*,[27, 29, 31] that excessive vomiting or postoperative gastric lavage may be associated with no intracellular changes or with any one of a variety of intracellular patterns such as (1) a decrease in potassium and increase in sodium, (2) an increase in sodium without a change in potassium, and (3) a decrease in potassium without an increase in sodium, demonstrates the variety of intracellular electrolyte patterns which may accompany the withdrawal of gastric juice. This probably means that other concomitant conditions influence the nature of the response to the induced deficit.

TABLE VI. *The Effects of Acute Hypochloremia Upon the Muscle Content of Water and Electrolytes (Per 100 Gm. Fat-Free Solids) and Their Distribution.*

Muscle per 100 Gm. Fat Free Solids						Distribution within extra- and intracellular position							
Patient	Diagnosis	H_2O Gm.	Cl mEq	Na mEq	K mEq	$(Cl)_i$ mEq./ 100 Gm. FFS (assumed)	$(Cl)_e$ mEq./ 100 Gm. FFS	$(H_2O)_e$ Gm. 100 Gm. FFS	$(H_2O)_i$ Gm. 100 Gm. FFS	$(Ne)_e$ mEq 100 Gm. FFS	$(Na)_i$ mEq 100 Gm. FFS	$[Na]_i$ mEq Kg. H_2O	$[K]_i$ mEq Kg. H_2O
1.	Normal.....	376	13.6	18.8	38.6	1.0	12.6	103	273	15.1	3.7	11	141
G.W.	Hypochloremia..	320	8.4	21.0	30.2	1.0	7.4	77	243	11.5	9.5	39	124
2.	Normal.....	400	14.7	19.0	42.2	1.0	13.7	129	271	20.0	−1.0	—	156
L.S.	Hypochloremia..	350	9.5	21.4	31.7	1.0	8.5	95	255	12.6	8.8	34	124
3.	Normal.....	365	12.8	19.5	38.6	1.0	11.8	101	264	14.5	5.0	19	146
V.C.	Hypochloremia..	300	7.8	22.6	27.1	1.0	6.8	84	216	10.8	11.8	55	126
4.	Normal.....	339	11.2	16.3	34.3	1.0	10.2	90	249	13.1	3.2	13	138
L.G.	Hypochloremia..	325	7.5	22.3	27.8	1.0	6.5	73	252	9.6	12.7	50	110
5.	Normal.....	388	13.6	17.8	41.7	1.0	12.6	118	270	16.7	1.1	4	154
J.C.	Hypochloremia..	339	8.3	25.4	23.0	1.0	7.3	90	249	13.1	12.3	49	92

These would include the electrolyte status of the patient,[49] the quantity and nature of fluid he is receiving during the period of gastric lavage,[38, 41] and the adrenal or other hormonal response,[37] and others.

An interesting observation was the nature of the extracellular water (plasma and interstitial volume) depletion. There was no correlation between the changes in plasma volume and that of the interstitial volume, suggesting that the interstitial fluid does not necessarily act solely as a reservoir to replenish plasma loss, but rather that both components can react semi-independently to altered hydration states.[33]

SUMMARY OF ELECTROLYTIC ALTERATIONS INDUCED BY WITHDRAWING GASTRIC JUICE

One may construe the sequence of events subsequent to the withdrawal of gastric contents containing an excess of chloride to be as follows. As the chloride is lost, the body attempts to conserve this ion, as reflected by the quantity excreted in the urine, which diminishes to the point where almost none is excreted. Body sodium combines with retained bicarbonate to maintain a state of electrolyte neutrality (hypochloremic alkalosis). This mechanism is either defective or temporary because sodium continues to be excreted in the urine in increasing amounts as the period of gastric lavage progresses. The third metabolic route of sodium observed in these experiments is its entrance into the cells. Associated with this ingress of sodium is an egress of potassium from within the cells.

These intracellular reactions are probably compensatory changes which in some way maintain the intracellular composition necessary for vital functions. The exchange of these two bases are semi-independent. Sodium cellular ingress does not always accompany potassium deficiency. Thus, in two patients with familial periodic paralysis studied by Elkinton, *et al.*, one patient showed reciprocal cellular changes of sodium and potassium and the other did not.[17] In infants with diarrhea, Darrow observed that half of them manifested inverse balances of cellular sodium, with depletion of cellular potassium.[20] Since the introduction of exogenous sodium does not enhance intracellular migration of the ion (Elkinton), it would appear that the sodium ingress is secondary to or probably the result of the extrusion of potassium from the cell. Whatever the explanation, the important clinical sequelae are that hypochloremic alkalosis is a powerful stimulus for producing a potassium deficiency. As the period of hypochloremia expands, and the potassium de-

ficiency becomes increasingly severe, a condition of hypokalemic alkalosis supervenes. The reason for the distinction in terminology is that in the first condition (hypochloremic alkalosis) the administration of sodium chloride solutions corrects the defect whereas, after hypokalemic alkalosis has developed, sodium chloride solution not only does not correct the abnormality, but intensifies it. The metabolic changes then are essentially the same as those produced by potassium deprivation.[27, 39, 59, 61]

TREATMENT OF ACUTE HYPOCHLOREMIC ALKALOSIS

In each of the patients studied, the administration of 0.9 per cent sodium chloride solution intravenously resulted in a prompt return to normal of the serum electrolytes. Figure 1 presents an example of this recovery. It is of great interest that the simple repair solution of sodium chloride can produce a normal state of serum electrolytes in the presence of a significant potassium depletion. It is well known that hypokalemic alkalosis will not respond to the administration of sodium chloride solutions; in fact, they apparently aggravate it. The correction of the hypochloremic alkalosis in these experiments suggests that the fundamental defect is within the extracellular space despite intracellular changes. Intake of potassium is necessary to correct this potassium defect, but it appears that during the condition of these rather acute experiments, the potassium deficiency is of secondary importance.

If the hypochloremic alkalosis persists for a prolonged period, the primary defect apparently shifts from the extra- to the intracellular position, which must be treated first. Unless potassium salts are administered before sodium chloride solutions, the disturbance will be aggravated by sodium chloride administration as it would be in any primary potassium deficient state. The quantities to be administered vary in different patients, and must be individualized. Thus, in the over-all appraisal of this disturbance, the time factor becomes of paramount importance, with emphasis upon the administration of adequate quantities of sodium chloride solutions during the early, acute phase of the deficiency, but potassium deficiency supervenes and must be corrected primarily if the disturbance persists over a prolonged period.

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