THE PARADOX OF ACIDURIA IN THE PRESENCE OF ALKALOSIS CAUSED BY HYPOCHLOREMIA*

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THE PARADOX OF ACID URINE excretion in the presence of internal alkalosis caused by loss of gastric juice is a phenomenon that has been recognized by a few investigators especially interested in the acid-base balance, but remains unfamiliar to most physicians. In this day of sulfonamide therapy and whole blood transfusions, with the accompanying increasing frequency of occasions when alkalinization of urine is considered desirable, it becomes pertinent to study the details of a condition in which a low urine pH does not indicate either the desirability or the safety of alkali administration.

An acid urine in the presence of internal alkalosis may be encountered whenever there is severe loss of gastric juice, as by vomiting or gastric suction. The paradoxical combination that results is a plasma of abnormally high pH and bicarbonate content, accompanied by a urine of low pH and practically no bicarbonate content.

The lost gastric juice contains both hydrochloric acid and chlorides of Na and K, chiefly Na.[1, 2] Loss of the sodium chloride and its equivalent of water causes dehydration. Loss of the hydrochloric acid causes part of the remaining plasma sodium chloride to be replaced by sodium bicarbonate, causing alkalosis to complicate the chloride loss and dehydration. In this condition, there is such a great depletion of body sodium salts that the kidneys cease to excrete sodium as either chloride or bicarbonate, despite the excessive plasma concentration of the bicarbonate. Urine lacking bicarbonate is acid.[3, 4] The condition encountered, therefore, is one in which an internal alkalosis, caused by loss of hydrochloric acid, is accompanied by excretion of acid urine.

As first noted by Haden and Orr in 1923,[5] bicarbonate administration in this condition is contraindicated because it increases the internal alkalosis and hastens the onset of tetany. If such a patient requires alkalinization of the urine, the preferable means is infusion of sodium chloride solution; this corrects the dehydration, sodium, and chloride deficit, decreases the internal alkalosis, and, at the same time, permits excretion of an alkaline urine; for alleviation of the body's deficit of sodium salts allows their excretion to be resumed. Of the excreted salts, part are in the form of bicarbonate, excreted from the excess present in the body, so that the urine pH rises. Sodium

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chloride infusion thus simultaneously alkalinizes the urine and restores the normal electrolyte pattern to the plasma and extracellular fluids of the body.

The concurrence of alkalosis and acid urine was produced experimentally in dogs in 1924 by Gamble and Ross,[2] who made a detailed study of the plasma and urine electrolyte changes and clearly discussed their significance. Hartmann and Smyth in 1926[6] studied the condition as produced by vomiting in patients, noting the concurrence of bicarbonate excess and chloride deficit in the plasma accompanied by acid urine; they attributed the acidity of the urine to non-excretion of sodium bicarbonate, which, they believed, occurred when the total "concentration of crystalloids" in the plasma was diminished. Several other authors, quoted by McCance and Widdowson[7] have noted the phenomenon, but it still appears not to have attained general recognition or understanding.

The present work supplements that of Gamble and Ross by providing additional studies of the experimentally induced condition, together with hour-by-hour observation of the blood and urine changes caused by sodium chloride and by sodium bicarbonate infusions. Control experiments have been done in which sodium chloride and sodium bicarbonate solutions were infused into normal dogs.

EXPERIMENTAL

Loss of gastric juice was produced in dogs by two methods: By the total gastric pouch method of Dragstedt,[8] and by gastrostomy combined with ligation of the pylorus. At the time of the original operation, an episiotomy was performed to permit easy catheterization during periods of urine collection. Daily intravenous 5 per cent dextrose solutions were infused during the three to five days required for body chloride depletion. When the plasma chloride concentration fell to below 70 milliequivalents per liter (400 mg. NaCl per 100 cc.) the dogs were considered to be sufficiently depleted of chloride for this study. Moderate or severe alkalosis, as determined by abnormally high plasma bicarbonate concentration, was invariably produced.

The dogs were then given intravenous infusions of either 0.9 per cent NaCl or 1.3 per cent $NaHCO_3$ at a constant rate of about 1000 cc. per three hours. These solutions are, in electrolyte concentration, isotonic with plasma and contain 1.15 times the sodium concentration of normal plasma. However, the chloride content of the isotonic NaCl infusion is about 1.4 times that of normal dog plasma, and the bicarbonate concentration of the $NaHCO_3$ infusion is about six times that of the normal plasma. In addition to these electrolytes, all infusions contained 5 per cent dextrose to stimulate the excretion of adequate urine volumes for chemical analyses.

Heparinized jugular venous blood samples were collected at 30–60 minute intervals throughout each experiment, the samples for CO_2 analysis being taken under oil. Consecutive 15–30 minute period urine samples were collected from an inlying catheter, with complete emptying of the bladder at the end of each period by air flushing except in experiments where urine was collected under oil for CO_2 analyses. Nembutal sedation was used only when necessary.

The following analytic methods were employed: plasma CO_2 content by the manometric method of Van Slyke and Neill,[9] plasma and urine chlorides by Van Slyke and Hiller's modification of the titrimetric silver iodate method of Sendroy,[10] urine pH by glass electrode, plasma and urine sodium and potassium by the flame photometer constructed by the Perkin-Elmer Corporation,[11] total plasma base by the electrodialytic method of Malm (unpublished) based on the procedure of Adair and Keys,[12] plasma protein by the copper sulfate specific gravity method of Phillips et al,[13] hematocrits by centrifugation.

For presenting and plotting the results, values for chloride, bicarbonate, sodium, total base, potassium, and R^2 are expressed in milliequivalents per liter of the ions, Cl, HCO_3, Na, etc., rather than in grams of their respective salts. The use of milliequivalents facilitates comparison of the concentrations and changes in the different electrolytes. Normal dog plasma contains about 150 to 158 mEq/L of total base, the distribution being about 140 mEq/L of Na, 5 of Ca, 5 of K, and 3 of Mg. These cations are balanced by 105 to 115 mEq/L of Cl, 20–25 of HCO_3, about 16 of protein, and the remainder by a residual sum, indicated by the symbol R, comprising SO_4, HPO_4, and unidentified anions. The sum of $Cl + HCO_3$ usually approximates the Na, except in starvation or dehydration when the R factor may be large. The only marked difference noted between the plasma electrolytes of man and the dog is that the chloride in the dog averages about 10 mEq/L higher than in man. The "isotonic" 0.9 per cent NaCl solution used for injections contains 154 mEq/L of Na and Cl, and the "isotonic" 1.3 per cent $NaHCO_3$ contains 154 mEq/L of Na and of HCO_3.

The experiments presented below are selected as examples from 20 experiments that yielded similar results.

RESULTS

With only two exceptions in 20 experiments (experiments 3 and 4 in this paper) all the hypochloremic dogs (46–65 mEq/L plasma chloride concentration) showed the paradox of aciduria (urine pH 5–6) in the presence of moderate to severe alkalosis (plasma CO_2 35–51 mM/L.). Infusion of solutions of either sodium chloride or sodium bicarbonate into such dogs increased the urine pH. Sodium chloride infusion raised the urine pH in some cases as high as 7.8. Sodium bicarbonate infusions raised it as high as 8.4. Little or no rise of urine pH occurred when a hypochloremic dog was given intravenous 5 per cent dextrose solution, and sodium chloride infusion into normal dogs caused a fall in urine pH.

Experiment 1. The Effect of Infusing 0.9 Per Cent NaCl + 5 Per Cent Dextrose Intravenously Into Hypochloremic Dog. (Fig. 1a, 1b, 1c, 1d, Table I).

This experiment was conducted four days after gastrostomy and pyloric ligation of a 43-pound dog. Plasma analyses (see Table I) immediately prior to the saline infusion showed the dog to be in a state of extreme hypochloremia (plasma Cl 45.6 mEq/L), alkalosis (plasma HCO_3 49.9 mEq/L),* total base deficiency (plasma total base 137.3 mEq/L) and sodium deficiency (plasma sodium 125.5 mEq/L). Unfortunately, an

* HCO_3 concentrations in this paper are calculated from plasma CO_2 measurements by assuming a plasma pH of 7.5.

adequate pre-infusion urine sample was not obtained, for the dog had a tetanic convulsion and emptied her bladder just before the infusion was begun. The preliminary urine was undoubtedly acid, for the urine pH was 5.3 an hour after the infusion was started and the urine of almost all other hypochloremic dogs was acid.

During a 12-hour period, 4670 cc. of 0.9 per cent NaCl in five per cent dextrose solution was infused intravenously at a constant rate of 90–100 drops per minute. Small doses of intravenous nembutal controlled restlessness without putting the dog to sleep. Urine was collected in 30-minute periods under oil. Hourly jugular blood samples were also collected under oil. The infusion was continued 12 hours.

During the 12-hr. infusion 2853 cc. of urine were excreted (see Figure 1d), while 1817 cc., 38.9 per cent, of the infused water was retained. Of the 42 Gm. of NaCl infused, 11 Gm. were excreted and 31 Gm., or 74 per cent, were retained. 5.6 Gm. of $NaHCO_3$ (66.5 millimoles) were excreted during the experiment; this is equivalent to about 2.8 times the total grams of $NaHCO_3$ in the plasma of a normal dog of this animal's weight, and more than even this alkalotic animal had in her plasma at the beginning of the infusion. Obviously a good deal of the excreted sodium bicarbonate came from the interstitial fluids.

Figures 1a and 1b and table I show in detail the manner in which the intravenous sodium chloride infusion corrected both the hypochloremia and the alkalosis caused by gastric fluid loss. There is a striking return of the plasma acid-base balance to normal. Plasma Cl concentration rose from 45.6 mEq/L to the normal 110.0 mEq/L. Plasma bicarbonate fell from 49.9 mM/L to 27.7 mM/L. Plasma total base rose from 137.3 mEq/L to 154.0 mEq/L and plasma sodium from 125.5 to 150.0 mEq/L. Undeterminable anions,* Gambel's R factor[2] fell from 18.5 mEq/L to 3.1 mEq/L. During the last three hours of the infusion the hematocrit and the concentrations of protein, chloride, and bicarbonate in the plasma remained nearly constant at normal levels, indicating that the body's water and chloride deficits, and its bicarbonate excess, had been corrected.

The decrease in plasma bicarbonate concentration was partly due to the bicarbonate excretion discussed above; but in part it was attributable to dilution of the plasma and interstitial fluids with the infused 154 millimolar NaCl solution, which contained no bicarbonate and three times the plasma's Cl concentration. Dilution of the body's extracellular fluids with this chloride solution would obviously raise the Cl and lower the HCO_3 concentration. This dilution effect is shown by the rise of Cl and fall of HCO_3 in the plasma during the first three hours of the infusion, when practically no chloride or bicarbonate was being excreted.

Figures 1c and 1d and Table I show strikingly the way in which correcting the internal sodium chloride deficit released the excess bicarbonate for excretion, and in so doing raised the urine pH. When, after the third hour of infusion (1010 cc., 9 Gm. NaCl), excretion of sodium salts began to be accelerated, the first salt to be excreted was not chloride, but bicarbonate (Fig. 1c). From the third to the seventh hour the urine contained more bicarbonate than chloride. Then, plasma chloride having been doubled and plasma bicarbonate lowered by a third (Fig. 1a), urinary chloride concentration began to surpass bicarbonate.

The effect of the rise in urine bicarbonate in raising urine pH is shown by the parallelism of the pH and HCO_3 concentration curves in Figure 1c. Rise of urine bicarbonate concentration from 0.7 to its maximum of 44.1 millimoles per liter raised the pH from 5.3 to its maximum of 7.8. Thereafter, bicarbonate excretion continued in somewhat lower, but still rather high concentration, and urine pH continued at 7.42–7.68.

* R factor, the undeterminable anions, is determined by subtracting the sum of base combined with Cl, HCO_3, and proteins from the total base. In these experiments the base combined with proteins is calculated: B protein $=0.234 \times$ Gm. per cent protein assuming a normal A/G ratio of 1.8 (14). Total base determinations, by the electrodialysis method employed, do not include Mg^{++}.

Chloride excretion was insignificant until the plasma chloride concentration reached 80 mEq/L. As the plasma chloride concentration rose above 80 mEq/L the rate of chloride excretion rose with it; the threshold level of plasma chloride was therefore about 80 mEq/L in this experiment.

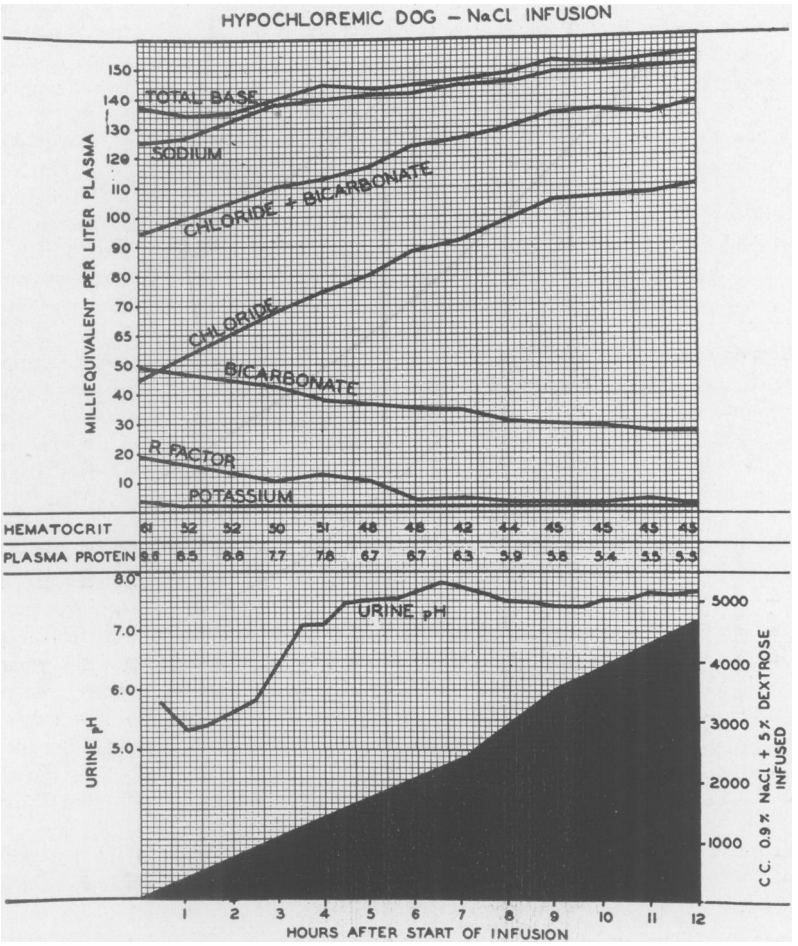

FIG. 1A.—Showing the effect of 0.9 per cent NaCl + 5 per cent dextrose infusion on the plasma electrolyte pattern of a hypochloremic alkalotic dog. Note that, despite the fall in plasma bicarbonate concentration the urine pH rises as the body NaCl deficit is corrected.

At the start of this experiment the plasma *potassium* concentration was 3.9 mEq/L (normal 4.5–5.0 mEq/L). This potassium deficit is consistent with the observations of Gambel and McIver[1] that cat and dog gastric juice contains up to 50 mg. per cent of potassium and with the observation of Elkinton and Winkler[15] that dehydration in itself is likely to diminish the potassium supply of the body.

Within an hour after the start of the sodium chloride and dextrose infusion the plasma potassium fell to 2.0 mEq/L and thereafter it remained below 2.7 mEq/L. Similar washing out of plasma potassium by infused sodium chloride solution has been reported in experiments by Flock[16]; and recently Holler[17] and Martin and Wertman[18] have clinically observed reduction of plasma potassium to paralytic levels in diabetic

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TABLE I

HYPOCHLOREMIC DOG

0.9% NaCl + 5% DEXTROSE I. V. INFUSION

Procedure					Plasma									
Minutes after start of infusion	Volume infused (cc)	NaCl infused (Gm.)	Blood and Urine Samples		Sample	Hemato-crit %	Total Protein Gm. %	Cl mEq/L	HCO_3 mM/L	Cl + HCO_3 mEq/L	R	Na mEq/L	K mEq/L	Total base mEq/L
−15	0			U_0										
0	0		Bc	Uc	Bc	60.5	9.61	45.6	49.9	95.5	18.5	125.5	3.9	137.3
30	200	1.8		U_1										
60	360	3.2	B_1	U_2	B_1	52.2	8.50	53.6	lost	.....	....	127.5	2.0	134.9
90	615	5.5		U_3										
125	700	6.3	B_2	U_4	B_2	52.4	8.61	60.5	lost	.....	....	133.0	...	135.7
150	850	7.6		U_5										
180	1010	9.1	B_3	U_6	B_3	50.4	7.73	68.2	42.8	111.0	10.2	138.5	2.1	140.0
210	1180	10.6		U_7										
240	1360	12.2	B_4	U_8	B_4	51.3	7.80	75.0	38.3	113.3	12.6	140.0	2.1	144.8
270	1500	13.5		U_9										
300	1680	15.1	B_5	U_{10}	B_5	47.5	6.67	80.0	36.9	116.9	10.4	141.5	2.7	143.5
330	1860	16.7		U_{11}										
360	....	....	B_6	U_{12}	B_6	47.5	6.67	88.8	35.3	124.1	4.0	142.0	2.2	144.3
390	2190	19.7		U_{13}										
420	2370	21.3	B_7	U_{14}	B_7	46.5	6.28	92.0	34.4	126.4	4.5	144.5	2.5	146.2
450	2680	24.1		U_{15}										
480	2940	26.4	B_8	U_{16}	B_8	43.8	5.90	99.0	30.8	129.8	3.7	145.5	2.2	147.8
520	....	....		U_{17}										
550	3520	31.7	B_9	U_{18}	B_9	44.9	5.83	105.5	29.1	134.6	3.6	148.5	...	152.4
570	3660	32.9		U_{19}										
600	3870	34.8	B_{10}	U_{20}	B_{10}	44.6	5.35	106.5	29.0	135.5	3.2	148.5	2.2	151.7
630	4130	37.1		U_{21}										
660	4290	38.6	B_{11}	U_{22}	B_{11}	44.5	5.54	107.1	27.4	134.5	4.6	149.0	2.2	152.6
690	4470	40.2		U_{23}										
720	4670	42.0	B_{12}	U_{24}	B_{12}	44.7	5.50	110.0	27.7	137.7	3.1	150.0	2.2	154.0

TABLE I (cont.)

HYPOCHLOREMIC DOG

0.9% NaCl+5% DEXTROSE I. V. INFUSION

Urine

Sample	Volume cc./period	Volume cc./min.	pH	Chloride Concentration mEq/L	Chloride Excretion mEq/min.	NaCl Excretion mg/period	Sodium Concentration mEq/L	Sodium Excretion mEq/min.	CO_2 mM/L	HCO_3 Concentration mEq/L	HCO_3 Excretion mEq/Min.	$NaHCO_3$ Excretion mg/period
Uc	3											
U_1	15	0.50	5.9	0	0	0	4	0.002	1.9	0.7	0.0	1
U_2	41	1.36	5.3	0	0	0	4	0.005	1.4	0.2	0.0	1
U_3	54	1.80	5.4	0.5	0.001	2	13	0.023				
U_4												
U_5	152	2.54	5.8	0.5	0.001	4	17	0.043	1.8	0.6	0.002	10
U_6	96	3.20	6.4	0.5	0.002	4	26	0.083	5.2	3.5	0.001	28
U_7	93	3.10	7.1	1.5	0.005	8	39	0.121				
U_8	119	3.97	7.1	3.0	0.012	21	48	0.190	26.3	23.9	0.095	425
U_9	103	3.44	7.45	3.4	0.012	21	48	0.165				
U_{10}	116	3.87	7.54	5.6	0.022	38	52	0.201	32.9	31.6	0.122	582
U_{11}	130	4.34	7.56	14.2	0.062	76	65	0.282				
U_{12}	148	4.94	7.65	26.5	0.131	231	70	0.345	40.2	38.9	0.194	910
U_{13}	66	2.20	7.80	36.8	0.081	142	74	0.163				
U_{14}	100	3.33	7.76	42.2	0.147	246	78	0.252	45.0	44.1	0.147	616
U_{15}	125	4.13	7.63	57.2	0.236	418	87	0.363				
U_{16}	206	6.87	7.50	68.0	0.467	806	87	0.598	26.4	25.2	0.175	702
U_{17}	172	4.30	7.49	89.5	0.385	900	94	0.404				
U_{18}	318	10.60	7.42	115.0	1.220	2140	104	1.110	20.4	19.5	0.207	803
U_{19}	92	4.60	7.43	118.5	0.543	638	130	0.598				
U_{20}	157	5.24	7.52	121.9	0.639	1119	144	0.754	20.9	20.1	0.105	421
U_{21}	132	4.40	7.54	124.3	0.547	959	152	0.669				
U_{22}	136	4.54	7.68	128.5	0.584	1022	152	0.690	23.2	22.5	0.102	507
U_{23}	144	4.80	7.61	130.0	0.624	1095	152	0.730				
U_{24}	135	4.50	7.65	134.0	0.643	1113	152	0.684	25.3	24.6	0.106	577
	2853 cc.					11.0 Gm.						5.6 Gm.

patients treated with large infusions of intravenous dextrose and sodium chloride. It is possible that some of the potassium is deposited into the liver and muscle with glycogen formed from the infused dextrose, as postulated by Fenn.[19]

That paralysis did not develop may be due to the simultaneous loss of calcium Though direct calcium determinations were not made in this experiment, the difference between total base and the Na + K in the plasma during the infusion fell so low that it appears that calcium must have fallen much below the normal 5 mEq/L. Since neither tetany nor paralysis occurred, the possibility suggests itself that simultaneous calcium

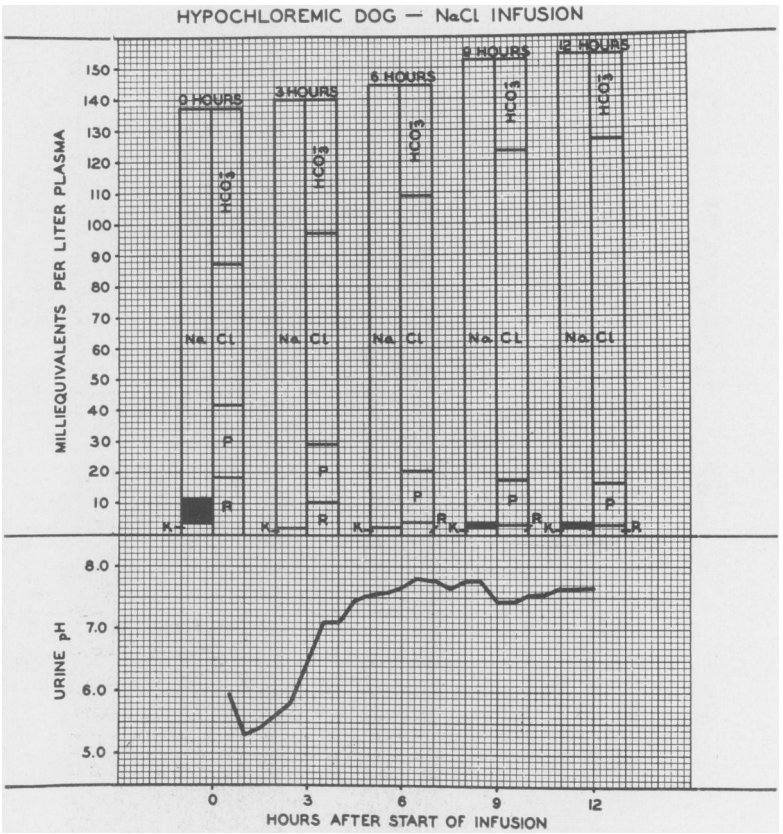

FIG. 1B.—Showing the effect of 0.9 per cent NaCl + 5 per cent dextrose infusion on the plasma electrolyte pattern of a hypochloremic alkalotic dog. Note that, despite the fall in plasma bicarbonate concentration, the urine pH rises as the body NaCl deficit is corrected. Also note the decrease in concentrations of cations other than sodium.

and potassium deficiency neutralized each other with regard to effect on muscle tone.

From this experiment, and from the clinical observations of others, it would seem advisable that a balanced electrolyte solution containing not only Na, but also Ca, K and Mg should be used when large electrolyte infusions are given.

This 43-pound dog excreted 5.6 Gm. of $NaHCO_3$ during the 12 hr. NaCl solution infusion. This bicarbonate excretion is equivalent to about 20 Gm. for a 70-kg. man. Since the body contained at least this much excess bicarbonate, it is apparent that bicarbonate administration was not indicated, despite the acid urine.

Experiment 2. The Effect of Infusing 0.9 Per Cent NaCl + 5 Per Cent Dextrose Intravenously Into Hypochloremic Dog. (Fig. 2, Table II).

This experiment practically duplicates the first three hours of Experiment 1, except that the initial plasma chloride deficit and bicarbonate excess were not quite so great (Cl 56.6 mEq/L, HCO_3 37 mM/L, compared with Cl 45.6 and HCO_3 49.9 in Experiment 1; sum of chloride plus bicarbonate nearly the same in both). The infusion, as that of the

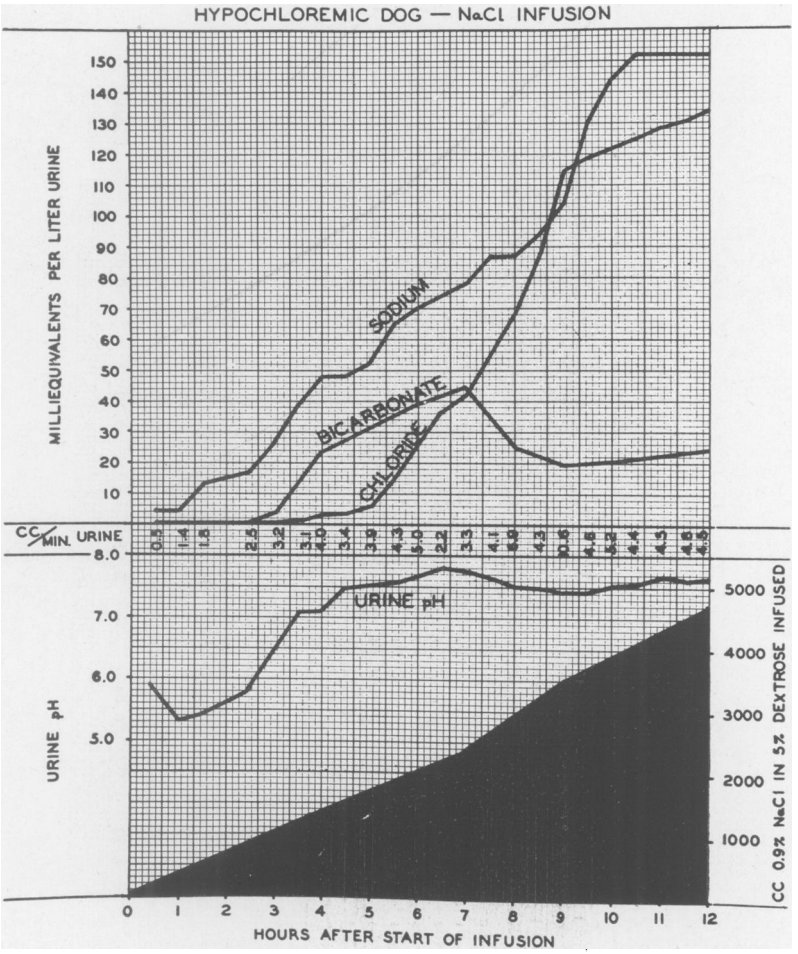

FIG. 1C.—Showing the effect of 0.9 per cent NaCl + 5 per cent dextrose infusion on the urine NaCl and $NaHCO_3$ concentrations of a hypochloremic alkalotic dog. Note that NaCl infusion frees a large amount of $NaHCO_3$ for excretion, and that urine pH parallels urine $NaHCO_3$ concentration.

first three hours of dog one, was insufficient to start significant excretion of water, chloride, or bicarbonate, the urinary HCO_3 concentration at the end of the three hours being sufficient only to raise the pH to 6.52. The initial dehydration of the dog is shown by the fact that during the three hours only eight per cent of the infused water was excreted. The partial correction of the plasma electrolyte picture (fall in HCO_3, rise in Cl and Na) is attributable, as in the first three hours of Experiment 1, to dilution of plasma and interstitial fluids with the infused 154 millimolar NaCl solution.

TABLE II

HYPOCHLOREMIC DOG

0.9% NaCl + 5% DEXTROSE I. V. INFUSION

Procedure				Plasma					
Minutes After Start of Infusion	Volume Infused (cc.)	Blood and Urine Samples		Sample	Hematocrit	CO_2 mM/L	Cl mEq/L	CO_2+Cl mEq/L	Na mEq/L
0	0	Bc	Uc	Bc		39.5	56.6	96.2	111
35	160	B_1		B_1	25	35.4	61.3	96.7	111
60	260	B_2	U_1	B_2	24	34.7	62.3	97.0	109
90	400	B_3		B_3	20	34.2	65.8	100.0	112
120	570	B_4	U_2	B_4	19	32.0	69.4	101.4	114
150	760	B_5		B_5	22	33.6	73.3	106.9	116
180	890	B_6	U_3	B_6	21	31.0	76.0	106.0	116

Urine									
	Volume			Chloride			Sodium			
Sample	cc./period	cc./min.	pH	Concentration Gm./L	Excretion Mg./min.	CO_2 mM/L	Concentration Gm./L	Excretion mg./min.	$NaHCO_3$ mg./period	NaCl mg./period
Uc			5.97	0	0	2.68	0.02			0
U_1	12	0.20	6.10	0	0	2.28	0.03	0.006	1.2	0
U_2	18	0.30	6.00	0	0	2.18	0.08	0.023	1.4	0
U_3	37	0.62	6.52	0.04	0.026	3.70	0.05	0.031	8.2	1.56
	67 cc.								10.8 mg	1.56 mg

Experiment 2 serves for comparison with Experiment 3 in which isotonic $NaHCO_3$ instead of NaCl was infused. In both experiments the initial dehydration, plasma Cl deficit and HCO_3 excess were nearly the same.

Experiment 3. The Effect of Infusing 1.3 Per Cent $NaHCO_3$ + 5 Per Cent Dextrose Intravenously Into Hypochloremic Dog. (Fig. 3, Table III).

In this experiment a salt depleted dehydrated dog was infused with an isotonic solution of sodium bicarbonate instead of sodium chloride. 900 cc. of 1.3 per cent sodium bicarbonate in five per cent dextrose solution were given during a three-hour period.

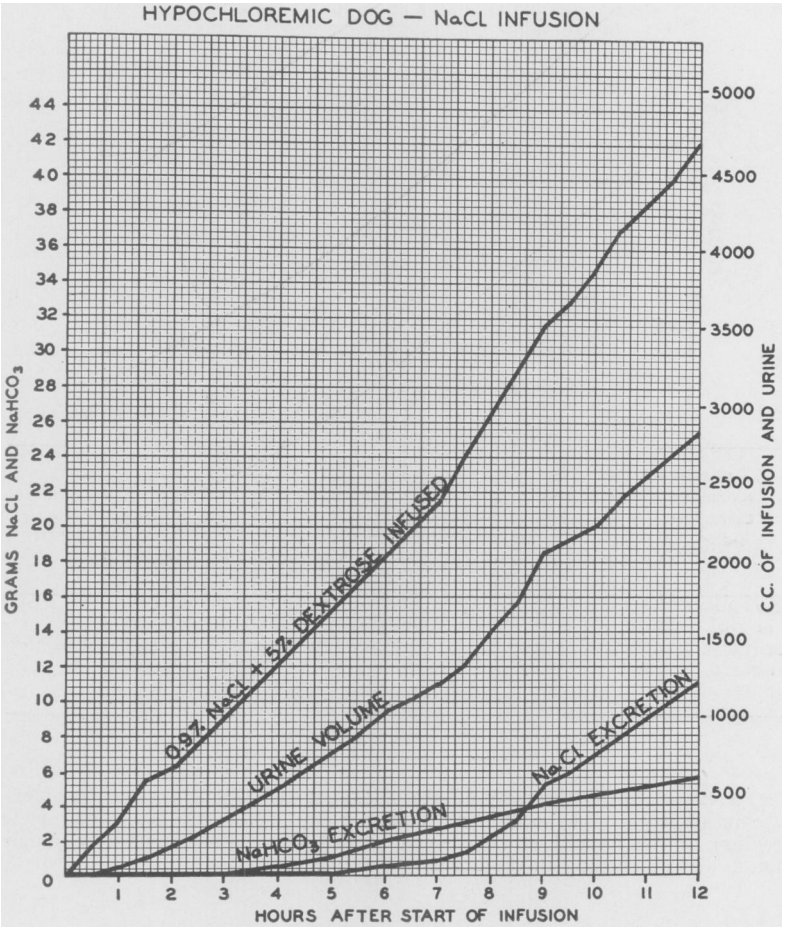

FIG. 1D.—Showing the total grams of NaCl and $NaHCO_3$ excreted by a hypochloremic alkalotic dog receiving intravenous 0.9 per cent NaCl + 5 per cent dextrose. Note that NaCl infusion frees a large quantity of $NaHCO_3$ for excretion.

Water excretion was more accelerated than in the previous experiments, the total urine excretion being 73 per cent of the infused solution, compared with eight per cent in Experiment 2. The diuresis was accompanied by a rapid increase in sodium salt excretion. The sodium excretion here was almost chloride free. The high bicarbonate content of the urine raised the pH above eight during most of the experimental period.

In this experiment, with sodium bicarbonate infusion, the infused sodium salt and water were less completely retained than in the preceding experiments where sodium chloride solution was infused. Of the sodium chloride infused during the previous experiments, only 0.0 to 0.1 per cent was excreted whereas of the sodium bicarbonate infused in this experiment, 38 per cent was excreted before the experiment finished.

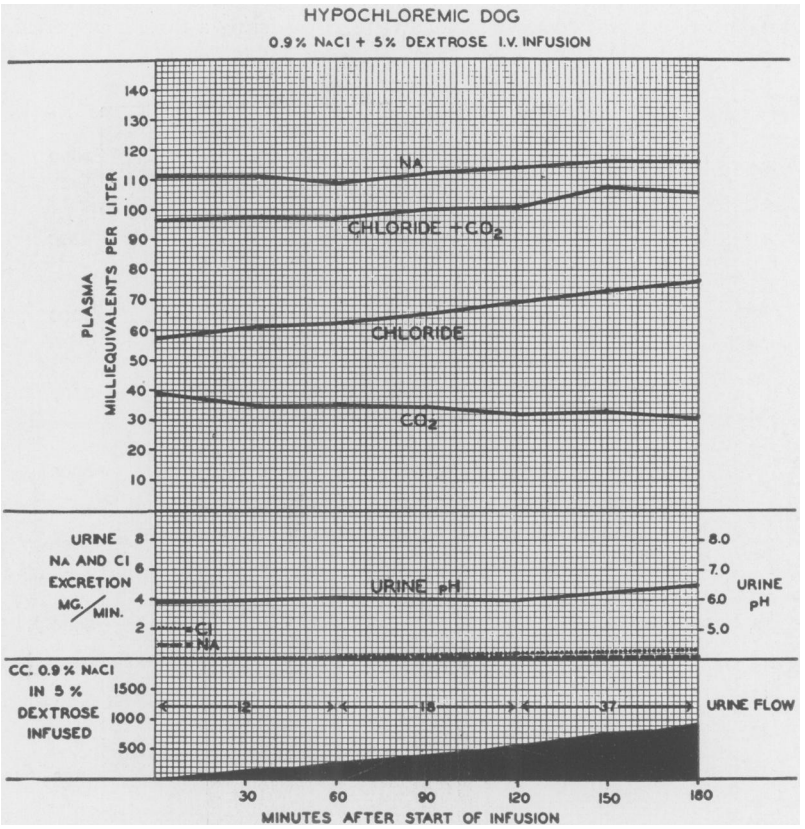

FIG. 2.—Showing the early effects of 0.9 per cent NaCl + 5 per cent dextrose infusion into a hypochloremic alkalotic dog. Note the almost complete retention of the infused saline causing plasma electrolyte changes by simple dilution and no changes in the urine.

It appears that the refusal of the kidneys to retain the infused bicarbonate may be attributable to the fact that the plasma bicarbonate concentration had already been raised by gastric hydrochloric acid loss to twice the normal level, and retention of bicarbonate would have increased the excess of that salt already present in the alkalotic organism.

The hypochloremic alkalotic plasma electrolyte pattern became even more marked during the bicarbonate infusion; chloride concentration fell, CO_2 rose, total base and R factor changed little. Thus the electrolyte imbalance was aggravated. This increasing alkalosis was accompanied by repeated convulsions necessitating intravenous nembutal.

The results indicate the undesirability of infusions of sodium bicarbonate in the state of hypochloremic alkalosis, even when accompanied by an initially acid urine.

TABLE III

HYPOCHLOREMIC DOG

1.3% $NaHCO_3$+5% DEXTROSE I. V. INFUSION

Procedure				Plasma							
Minutes after Start of Infusion	Volume Infused (cc.)	Blood and Urine Samples		Sample	Hematocrit %	Total Protein Gm. %	Cl mEq/L	HCO_3 mEq/L	Cl+HCO_3 mEq/L	Total Base mEq/L	R
0	0	Bc	Uc	Bc	58.4	7.8	60.1	34.2	94.3	129.2	15.9
30			U_1								
45	200	B_1		B_1	52.5		55.0	40.7	95.7		
60			U_2								
65	310	B_2		B_2	52.0		54.8	42.2	97.0		
90	420		U_3								
95		B_3		B_3	48.7	6.2	52.9	41.6	94.5	129.5	19.9
120	600		U_4								
127		B_4		B_4	48.3	5.9	52.6	47.0	99.6	128.2	14.3
150	750		U_5								
165		B_5		B_5	48.9	6.0	51.9	48.4	100.3	131.2	16.3
180	900	B_6	U_6	B_6	50.4	5.8	53.0	50.9	103.9	129.4	11.4

	URINE											
	Volume			Chloride		Total NaCl	Sodium			HCO_3		Total $NaHCO_3$
Sample	cc./period	cc./min.	pH	Concentration mEq/L	Excretion mEq/min.	Excretion mg./period	Concentration mEq/L	Excretion mEq/min.	CO_2 mM/L	Concentration mM/L	Excretion mM/min.	Excretion Gm./period
Uc	...	....	6.40	0	0	0	8.7	.....	2.2	1.1	.....	....
U_1	95	3.17	7.53	0	0	0	57.4	0.182	35.3	34.0	0.108	0.27
U_2	98	3.27	8.08	1.1	0.004	6.3	74.4	0.243	71.3	70.5	0.230	0.58
U_3	111	3.70	7.89	0.9	0.003	5.9	78.3	0.290	43.9	43.2	0.169	0.40
U_4	146	4.87	8.02	1.2	0.006	10.3	98.3	0.479	73.6	72.7	0.354	0.89
U_5	113	3.77	8.11	2.2	0.008	14.6	118.2	0.446	99.3	98.5	0.371	0.94
U_6	98	3.27	8.16	2.3	0.008	13.2	130.5	0.427	165.1	164.7	0.538	1.36
	661 cc.					50.3 mg.						4.4Gm.

TABLE IV

HYPOCHLOREMIC DOG

5% DEXTROSE IN WATER I. V. INFUSION

Procedure: Minutes After Start of Infusion	Volume Infused (cc.)	Blood and Urine Samples		Plasma: Sample	Hematocrit	Cl mEq/L	CO_2 mM/L	Cl+CO_2 mM/L	Na mEq/L
0	0	Be	Uc	Bc	45.7	64.6	40.1	104.7	120
25	110	B_1	U_1	B_1	43.2	61.0	39.4	100.4	115
60	290	B_2	U_2	B_2	42.0	58.6	37.2	95.8	112
90	430	B_3	U_3	B_3	40.8	57.4	35.0	92.4	109
120	620	B_4	U_4	B_4	41.8	56.4	37.9	94.3	103
150	790	B_5	U_5	B_5		54.9	37.5	92.4	
180	910	B_6	U_6	B_6	39.0	54.1	37.7	91.8	103

URINE

	Volume			Chloride		NaCl	Sodium	
Sample	cc./period	cc./min.	pH	Gm./L Concentration	mg/min. Excretion	mg/period Excretion	Gm./L Concentration	mg/min. Excretion
Uc	..	.....	6.72	0.025	....	....	0.048	...
U_1	16	0.64	6.51	0.039	0.02	1.03	0.050	0.03
U_2	58	1.7	6.54	0	0	0	<0.010	<0.02
U_3	45	1.5	6.90	0.014	0.02	1.02	<0.010	<0.02
U_4	88	2.9	6.90	0.007	0.02	1.01	<0.010	<0.02
U_5	61	2.0	7.15	0.007	0.01	0.70	<0.010	<0.02
U_6	54	1.8	7.19	0.019	0.03	1.69	<0.010	<0.02
	322 cc.					5.6 mg.		

TABLE V

NORMAL DOG

0.9% NaCl+5% DEXTROSE I. V. INFUSION

Procedure				Plasma				
Minutes After Start of Infusion	Volume Infused (cc.)	Blood and Urine Samples		Sample	Hematocrit %	Total Protein Gm. %	Cl mEq/L	CO_2 mM/L	$Cl+CO_2$ mEq/L
0	0	Bc	Uc	Bc	33.9	4.34	103.0	22.9	125.9
30	190	B_1	U_1	B_1	33.8	4.26	108.3	23.5	131.8
69	330	B_2	U_2	B_2	33.7	4.15	110.5	22.6	133.1
90	480	B_3	U_3	B_3	33.6	4.08	112.5	21.9	134.4
120	670	B_4	U_4	B_4	33.0	4.04	114.5	20.8	134.8
150	840	B_5	U_5	B_5	33.1	3.90	116.5	18.0	134.5
180	980	B_6	U_6	B_6	33.2	3.90	117.6	17.5	135.1

URINE

	Volume			Chloride		NaCl	Sodium			$NaHCO_3$		$NaHCO_3$
Sample	cc./period	cc./min.	pH	Gm/L Concentration	mg/min. Excretion	Excretion mg./period	Gm/L Concentration	mg/min. Excretion	CO_2 mM/L	Gm/L Concentration	mg/min. Excretion	Excretion mg./period
Uc	32	1.07	6.5	2.4	2.57	....	1.4	1.50	4.9	0.29	0.31	....
U_1	41	1.37	5.7	0.6	0.82	41.4	0.2	0.27	1.72	0.04	0.06	1.72
U_2	18	0.60	5.8	0.8	0.48	24.2	0.1	0.06	1.08	0.03	0.02	0.61
U_3	14	0.47	5.5	4.6	2.16	106.1	0.9	0.42	0.81	0.02	0.01	0.24
U_4	20	0.66	4.8	7.7	5.08	253.0	2.3	1.52	0.78	0.00	0.00	0.08
U_5	30	1.00	4.7	7.9	7.90	391.0	2.7	2.70	0.74	0.00	0.00	0.09
U_6	79	2.63	4.6	5.3	13.92	699.0	1.5	3.95	0.96	0.00	0.00	0.16
	234 cc.					1.51 Gm.						2.9 mg.

Experiment 4. The Effect of Infusing 5 Per Cent Dextrose In Water Into Hypochloremic Dog. (Fig. 4, Table IV).

This experiment serves as control for those in which NaCl plus dextrose or $NaHCO_3$ plus dextrose was infused. The dog received 910 cc. of solution in three hours and excreted 322 cc. of urine, or 35 per cent of the infused volume. The effects on plasma Cl, HCO_3 and Na concentrations are those of simple dilution by the retained water (hematocrit fell from 45.7 to 39.0 per cent). Excretion of Cl and Na were negligible. The urinary pH was raised only 0.4.

This control experiment shows that the rise in urine pH in Experiments 1, 2, and 3 was not the result of the glucose diuresis.

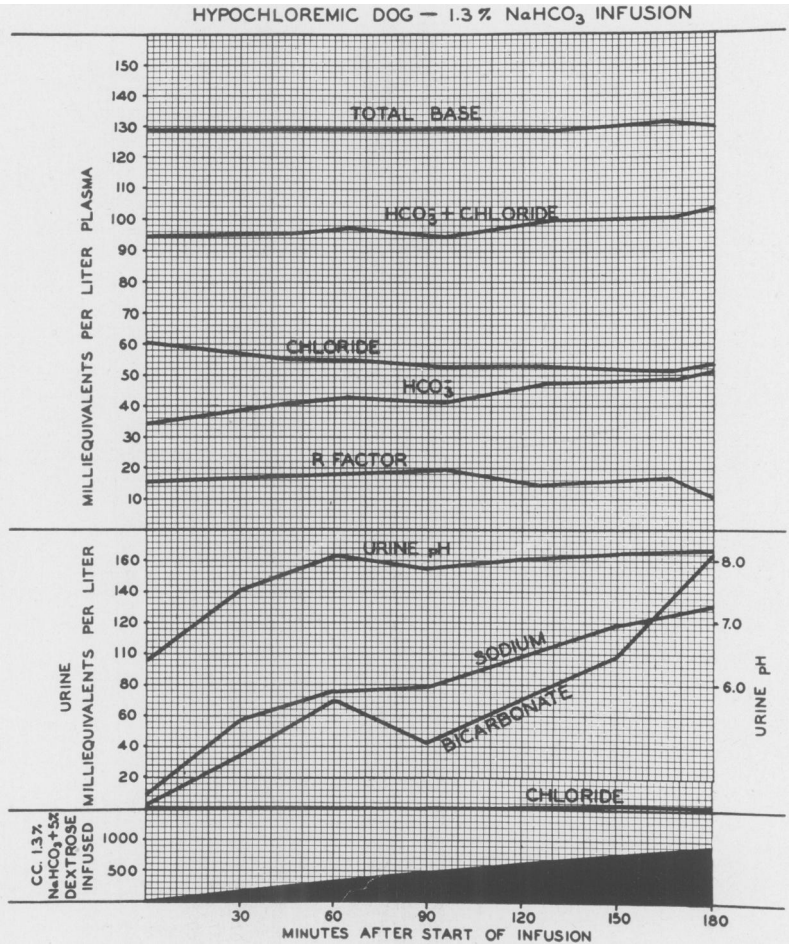

FIG. 3.—Showing the effects of 1.3 per cent (isotonic) $NaHCO_3$ + 5 per cent dextrose infusion into a hypochloremic alkalotic dog (compare with Fig. 2). Note the undesirable aggravation of the plasma anion imbalance and the failure to retain the infused solution.

This experiment shows: (1) that dextrose solution infused without salt into a dehydrated animal is not well retained (35 per cent of infused fluid was excreted during the three-hour infusion compared with eight per cent when 0.9 per cent NaCl was infused), (2) that such infusion does not correct the plasma chloride deficit nor, to a

TABLE VI

NORMAL DOG

1.3% $NaHCO_3$ 5% DEXTROSE I. V. INFUSION

Procedure				Plasma				
Minutes after Start of Infusion	Volume Infused (cc.)	Blood and Urine Samples		Sample	Hematocrit %	Cl mEq/L	Cl mM/L	Cl+CO_2 mEq/L
0	0	Bc	Uc	Bc	32.7	116.0	23.6	139.6
60	360	B_1	U_1	B_1	29.3	109.8	28.5	138.3
120	680	B_2	U_2	B_2	29.5	107.3	35.1	142.4
187	1020	B_3	U_3	B_3	30.5	104.1	38.7	142.8
240	1270	B_4	U_4	B_4	30.4	104.1	37.6	141.7
300	1570	B_5	U_5	B_5	29.3	102.2	38.2	140.6
340	1770	B_6	U_6	B_6	28.9	102.5	40.7	143.2

URINE

	Volume			Chloride			Sodium			HCO_3		
Sample	cc./period	cc./min.	pH	Gm/L Concentration	mEq/min. Excretion	NaCl Excretion mg./period	Gm/L Concentration	mEq/min. Excretion	CO_2 mM/L	gm/L Concentration	mEq/min. Excretion	$NaHCO_3$ Excretion mg./period
Uc	.. :	....	7.3	.. :	....	....	....	....	22.8	....	....	....
U_1	16	0.27	7.9	3.6	0.03	93.5	5.5	0.06	136	8.2	0.03	180
U_2	70	1.17	8.0	2.4	0.08	272	5.1	0.26	181	10.9	0.21	1050
U_3	143	2.14	8.1	1.7	0.10	395	3.9	0.36	140	8.5	0.30	1670
U_4	220	4.16	7.9	1.4	0.16	500	3.7	0.67	141	8.5	0.58	2440
U_5	252	4.20	8.0	1.2	0.15	492	3.4	0.62	143	8.6	0.60	3030
U_6	173	4.33	8.1	0.74	0.09	207	3.8	0.72	154	9.3	0.66	2220
	874 cc.					1.86 Gm.						10.6 Gm.

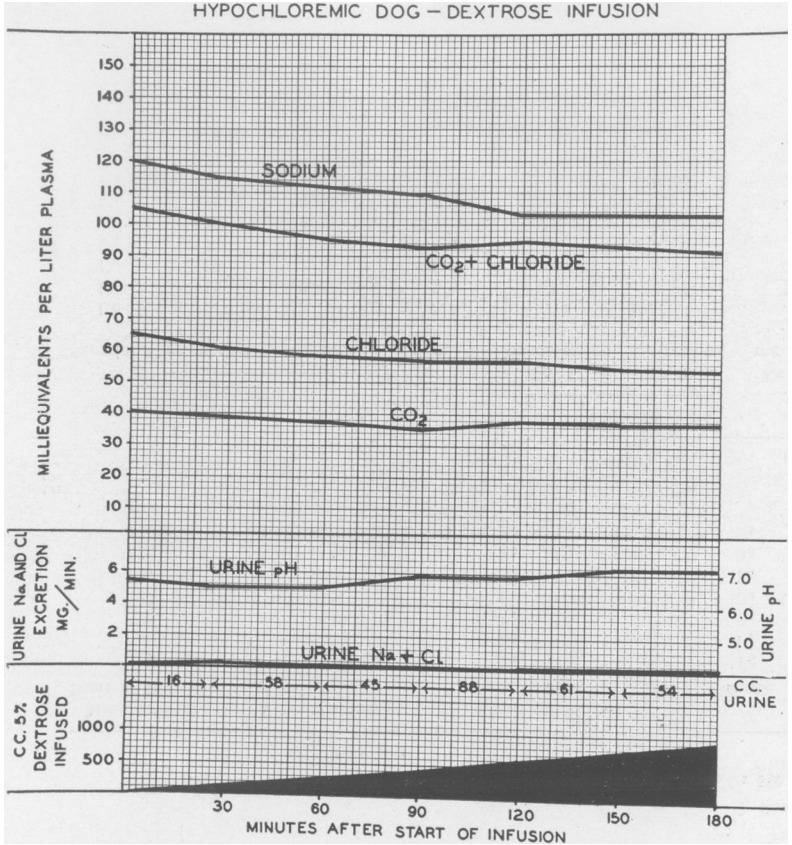

FIG. 4.—Control experiments showing the effects of five per cent dextrose infusion into a hypochloremic alkalotic dog. Note that the resultant diuresis does not raise the urine pH, and that the urinary effects of the NaCl dextrose and $NaHCO_3$ dextrose infusions in Experiments 1, 2, and 3 are not attributable to the infused dextrose.

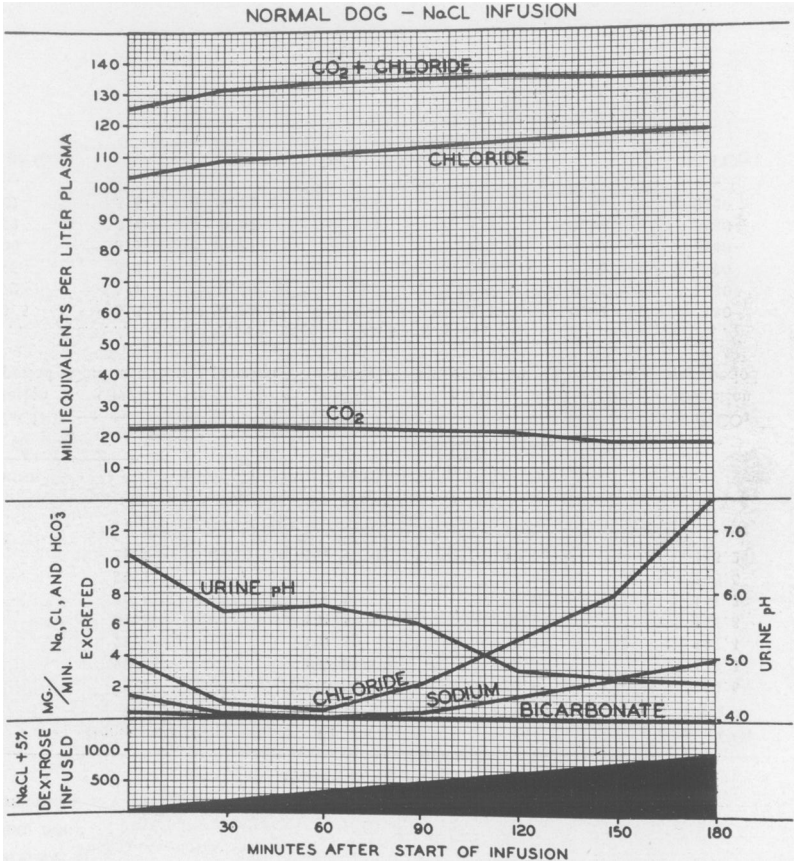

FIG. 5.—Control experiment showing the effects of 0.9 per cent NaCl + 5 per cent dextrose infusion into a normal dog. Compare with Figures 1, 2, and 3. Note the fall in urine pH caused by a dilution of the plasma bicarbonate to below its renal threshold concentration.

significant extent, the bicarbonate excess, and (3) that it does not accelerate bicarbonate excretion sufficiently to cause a marked rise in urinary pH.

Experiment 5. The Effect of Infusing 0.9 Per Cent NaCl + 5 Per Cent Dextrose Into Normal Dog. (Fig. 5, Table V). (Control Experiment).

In this experiment 980 cc. of a solution containing 0.9 per cent NaCl plus five per cent dextrose were infused intravenously during three hours, as in Experiments 1 and 2. Figure 5 shows the effects of diluting the plasma with 0.9 per cent sodium chloride

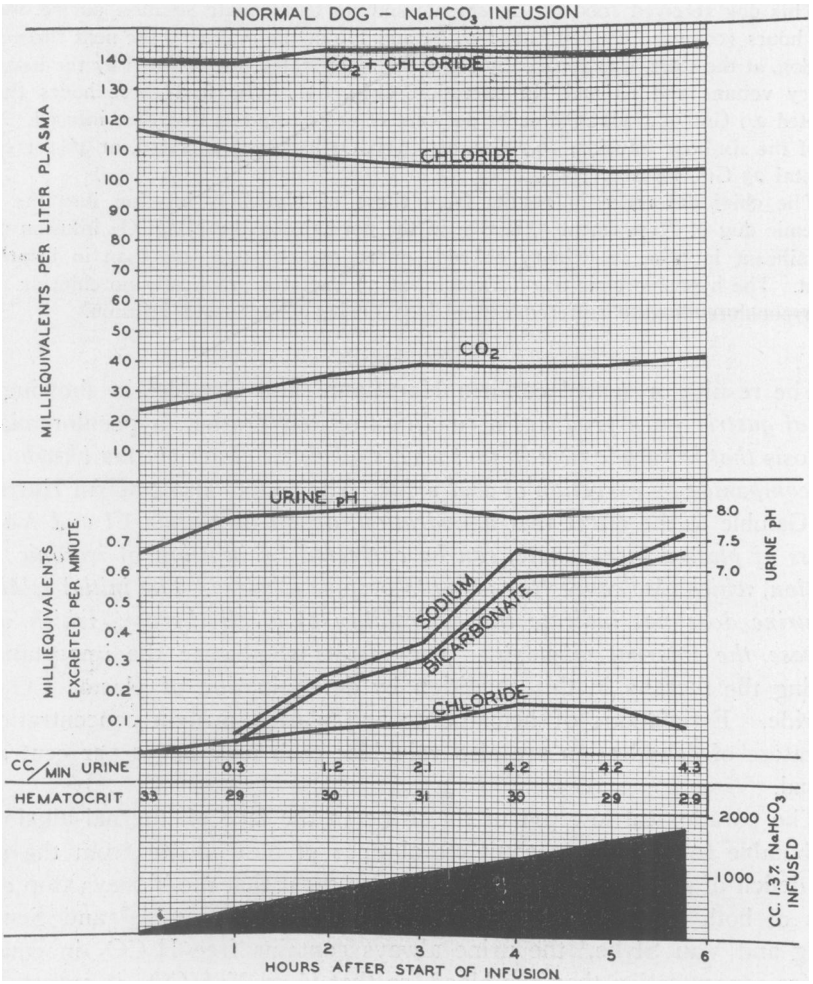

FIG. 6.—Control experiment showing the effects of 1.3 per cent (isotonic) $NaHCO_3$ + 5 per cent dextrose infusion into a normal dog.

solution (Cl concentration 154 mEq/L and CO_2 concentration 0); plasma chloride concentration rose 15 mEq/L and CO_2 fell from 22.9 to 17.5 mM/L.

Urine chloride concentration, after a peculiar fall in the first period, increased and reached 7.9 Gm/L, with a parallel increase in the rate of chloride excretion. The bicarbonate excretion rapidly fell to zero and remained there while the urine pH fell from 6.5 to 4.6. In this and other similar experiments the kidney bicarbonate threshold was

at about 20 mEq/L. Pitts,[20] under somewhat different conditions, found the bicarbonate threshold at about 25 mEq/L.

Comparison of this experiment with those of the hypochloremic dog reveals opposite effects on the urine pH. In the initially normal dog the urine pH falls as the plasma bicarbonate is decreased. In the hypochloremic dog, urine pH rises as the increasing plasma sodium chloride content releases the excess plasma sodium bicarbonate for excretion.

Experiment 6. The Effect of Infusing 1.3 Per Cent $NaHCO_3$ + 5 Per Cent Dextrose Into Normal Dog. (Fig. 6, Table VI).

This dog received 1000 cc. of isotonic sodium bicarbonate solution during the first three hours (compare Experiments 2 to 5) and 770 cc. more during the next three hours. The dog, at the start, was apparently somewhat dehydrated, as indicated by the low initial urinary volume and Cl and Na excretion (Fig. 6). The first three hours the dog excreted 2.9 Gm. of $NaHCO_3$, or 22 per cent of the amount at that time infused. At the end of the six-hour infusion, 10.7 Gm. of $NaHCO_3$ had been excreted, or 46 per cent of the total 23 Gm. infused.

The chief difference in results from those of $NaHCO_3$ infusion into the hypochloremic dog of Experiment 3, is that in the normal dog the $NaHCO_3$ infusion caused a significant increase in urinary chloride excretion, although less than in bicarbonate output. The hypochloremic dog (Experiment 3) excreted practically no chloride. Only the hypochloremic dog suffered convulsions during bicarbonate infusion.

DISCUSSION

The results presented confirm Hartmann[6] and Gamble[2] in showing that *loss of gastric juice produces a condition* of dehydration, hypochloremia and alkalosis *that is paradoxical in that severe alkalosis (high plasma bicarbonate) is accompanied by excretion of acid urine.* The results also confirm Hartmann and Gamble to the effect that *dehydration, deficit in plasma Cl and Na, and excess of plasma bicarbonate, can be corrected by infusion of isotonic NaCl solution, which also causes the urine to become alkaline. The initial acidity of the urine does not indicate the desirability of alkali therapy, which would increase the internal alkalosis.* The results emphasize the importance of guiding the therapy in this condition by determination of plasma CO_2 and chloride. Estimations of hematocrits and plasma protein concentration as indicators of dehydration are also valuable; each may be 50 per cent above normal.

The paradoxical low pH of the urine in the face of internal alkalosis is attributable to the almost complete absence of bicarbonate from the urine. The deficit of sodium salts in the body is so great that the kidneys stop excretions of both NaCl and $NaHCO_3$. As shown by Gamble[3] and Sendroy, Seelig and Van Slyke,[4] the urine always contains free H_2CO_3 in equal or greater concentration than the blood, so that if no $NaHCO_3$ is excreted, the pH will fall to that of a solution of such H_2CO_3 concentration, viz., about pH 5.

Infusion of NaCl, by correcting the body's deficit of sodium salts, permits excretion of $NaHCO_3$ and rise of urine pH. One encounters another apparent paradox in that infusion of neutral NaCl solution causes excretion of alkaline, bicarbonate-containing urine.

The results of Experiment 1 and 2, with infusion of NaCl into dogs

suffering from dehydration, chloride deficit and alkalosis from loss of gastric fluid also show that:

1. In severe dehydration from loss of gastric juice, NaCl infusion corrects the abnormalities of the plasma electrolyte pattern by three mechanisms: (a) the lost sodium chloride and water are replaced, (b) the excessive bicarbonate concentration in plasma and interstitial fluids is decreased by dilution with the infused chloride solution and (c) plasma bicarbonate is further lowered by excretion of bicarbonate in the urine in large amounts.
2. To complete the correction of the plasma pattern, large amounts of NaCl solution must be infused. To restore plasma Cl and HCO_3 to approximately normal concentration, the 20-kg. dog in Experiment 1 required 3 liters of 0.9 per cent NaCl solution, or 150 cc. per kg., which was infused during the first eight hours.
3. Reappearance of chloride in the urine could not be used as indication that enough saline had been infused to correct the plasma electrolyte pattern. In Experiment 1, after infusion of 100 cc. of 0.9 per cent NaCl per kg., chloride concentration in the urine reached 20 mEq/L. (0.71 Gm. per liter) when plasma chloride was still only 90 mEq/L (compared with normal dog's 110–120) and plasma bicarbonate was 36 mM/L (normal 20–25). It was only towards the end of the infusion, when chloride concentration in the urine reached about 100 mEq/L (6 Gm. NaCl per liter), that plasma values approached normal (Cl 105 mEq/L, HCO_3 29 mM/L), and they were still not quite back to normal. *When normal plasma electrolyte pattern was approached, the urine Na concentration rose to a level equal to that of the infused fluid (154 mEq/L), and the sum of urinary $Cl + HCO_3$ concentration also approximated 154 mEq/L.*
4. During the large NaCl infusion of Experiment 1, the concentration of cations other than sodium and magnesium (total base concentration—sodium concentration fell from 12.2 mEq/L to 4.0 mEq/L.) Plasma potassium determinations showed a fall from 3.9 to 2.2 mEq/L. These results suggest when large volumes are infused, that it is advisable to use a balanced infusion solution of $NaCl + KCl + CaCL_2 + MgCl_2$ instead of simple NaCl solution.

An unexpected point of interest is the apparent difference in the plasma thresholds for excretion of chloride and sodium in dogs that are passing from normal hydration to dehydration, compared with dogs that are passing in the opposite direction, from the dehydration (caused by loss of gastric juice) to normal hydration by saline therapy. In the normal dogs, we have seen a 24-hour fastnig period cause almost complete suppression of Na and Cl excretion, although the plasma Cl was still at the normal level of 110–115 mEq/L, and $Cl + HCO_3$ at 140. When hypochloremic dehydrated dogs were infused with NaCl, however, chloride excretion started by the time the plasma chloride had reached 80 mEq/L, and plasma $Cl + HCO_3$ was not over 120 mEq/L (Experiment 1). The kidneys in the salt depleted dogs had apparently lowered their chloride threshold and, when the chloride depletion was in process of correction by saline infusion, the kidneys began to excrete salt much before the normal plasma level was regained. A diagnostic corollary appears

to be, that when a condition of salt depletion is being established, drop of chloride excretion to a low rate is a more sensitive indicator of the condition than is the plasma chloride concentration. But when the condition of depletion of the type caused by loss of gastric juice is in process of correction by NaCl administration, restoration of normal plasma chloride concentration shows more accurately than resumption of chloride excretion when enough saline has been given to correct the condition.

SUMMARY

The condition of dehydration, hypochloremia and alkalosis, observed after severe loss of gastric juice by vomiting or gastric suction, has been reproduced in dogs by the total gastric pouch method of Dragstedt and by gastrostomy with pyloric ligation.

Despite the alkalosis (excess plasma bicarbonate) the urine was acid (pH 5 to 6.4). The acidity of the urine is attributed to the fact that the body deficiency of sodium salts is so great that excretion of both NaCl and $NaHCO_3$ is almost completely stopped, in the apparent effort to preserve what is left of the body's store of sodium salts. In the absence of bicarbonate in the urine, the pH falls towards that of a solution of free H_2CO_3.

Sodium chloride infusions corrected the alkalosis and dehydration, replaced the lost plasma sodium and chloride, and permitted excretion of the excess $NaHCO_3$, which raised the urine pH to 7.5–8.0.

During saline infusion resumption of chloride excretion was not a safe sign of adequate replacement; replacement was adequate only when plasma chloride concentration was restored to a normal level.

Massive infusion of a solution of NaCl plus glucose was observed to decrease the plasma potassium to less than half the normal concentration, and, by indirect estimation, also the calcium. These effects indicate the desirability of using a balanced electrolyte solution of Na, K, Ca, and Mg when large infusions are given.

Sodium bicarbonate infusion did not correct the plasma electrolyte pattern, raised urinary pH above the physiologic range (pH 8), and caused tetanic convulsions.

The results indicate the possible dangers of using sodium bicarbonate to alkalinize the urine of patients suffering gastric fluid loss, the advisability of using NaCl infusions, and the desirability of guiding the therapy by plasma analyses including at least chloride and CO_2 determinations.

We wish to express our appreciation to Dr. Ole Malm and to Dr. Howard Eder for determining the plasma total base, sodium, and potassium concentration in experiments 1 and 3, and to Dr. D. D. Van Slyke for his great help in analyzing and discussing the data presented.

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