

CALCIUM CHLORIDE ACIDOSIS.

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GYÖRGY⁽¹⁾ has shown that calcium chloride, when administered to babies, causes an increased ammonia and acid output in the urine. The experiment here described was made on J. B. S. H. (100 kilos) and lasted for 13 days, during three of which he drank 85 grams ($\cdot 766$ gram-molecule) of calcium chloride in 3.5 litres of water. The food intake was approximately constant through the experiment. The water intake, where above normal, is shown in the table.

Alveolar carbon dioxide was estimated by the Haldane-Priestley method, each daily value being the mean of four pairs of samples. In the urine pH was estimated with Clark-Lubs indicators and buffer mixtures, acid excretion by titration to pH 9 with $\cdot 1 N$ soda and thymol blue, buffer excretion by titrating back to pH 3.7 with $\cdot 1 N$ hydrochloric acid and thymol blue. A small correction, rarely exceeding .1 p.c., was made for the acid uncombined at the latter reaction. Ammonia was estimated by van Slyke's⁽²⁾ method, phosphates with uranium acetate, chloride by Volhard's, and calcium by McCrudden's⁽³⁾ method. A Cole-Onslow⁽⁴⁾ comparator was used when necessary. Faecal carbonate was estimated as carbon dioxide in J. S. Haldane's⁽⁵⁾ blood-gas apparatus, faecal phosphorus with uranium acetate after boiling with nitric and sulphuric acids.

In order to bring $\cdot 05 N$ ammonium chloride solution to pH 9 it was found necessary to add 16 p.c. of its equivalent of $\cdot 1 N$ soda, the salt being partly hydrolysed, while on subsequent addition of formaldehyde only 85 p.c. of its equivalent was needed to bring it back to pH 9. Hence if we add the ammonia and acid excretions found in this research, we obtain a value for the total acid eliminated free and in combination with ammonia which is too high by 16 p.c. of the ammonia value. 16 p.c. of the ammonia values have therefore been subtracted from the acid excretion, and the result given as "net acid." If the ammonia is titrated with formaldehyde the total value is correct, except for the small error due to amino-acids, but the ammonia values are too low. The buffering

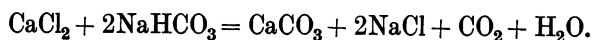
between pH 9 and 3.7 is due in part to the hydrolysed fraction of the ammonia, in part to phosphates, each molecule of which buffers one equivalent of acid. The buffer excretions when these values have been deducted are given as "undetermined buffers." Urines were collected in 12 hour periods from 9.30 to 9.30. Quantities ingested and excreted are given in milligram-molecules, or c.c. N solution per 12 hrs.

Calcium chloride in 3 p.c. solution produced no nausea, but there was intense diarrhoea, followed by constipation due to the formation of a large hard faecal mass. There was great general discomfort, pains in the head, limbs and back, and disturbed nights. These effects never occur with ammonium chloride, and must be attributed to the calcium. The alveolar carbon dioxide fell, while acid, ammonia, and phosphate excretion rose, their relations being similar to those found by Haldane(6) in ammonium chloride intoxication and leaving no doubt that an acidosis is produced. The cH soon reached its maximum, followed by acid and phosphate excretion, and slightly later by ammonia and the carbon dioxide minimum. The ammonia excretion was still four times normal when the acid and phosphate had returned to their usual values. This was due to a depletion of the phosphate available for excretion, whilst there were still sources for ammonia. The same cause accounts for the exaggerated diurnal drop in phosphate excretion. The pH fell to a fairly steady minimum value of 4.9 comparable to that of 4.7 recorded by Henderson and Palmer(7). It is probably analogous to the maximal concentrations of urea, chloride, and bicarbonate found by Ambard and Papin(8) and Davies, Haldane and Peskett(9). Its early fall may betoken renal fatigue. There was no evidence of a maximal concentration of any other constituent being reached, though on the night of the 20th-21st the ammonia reached .250 N and the acidity .131 N . The buffers varied greatly, the undetermined buffers much less, the extreme values for daily excretion being 75.9 and 57.4, though the results of the 25th suggest that they can be washed out by drinking. Their relative steadiness is intelligible since the most important weak electrolytes in urine unanalysed here are uric acid and creatinine. The phosphates on the average only contributed one-third of the total buffering power, while the ammonia occasionally contributed more than the phosphates.

The calcium excretion fell to nearly normal figures within 12 hours of the last salt being taken. The extra calcium in the urine before this time accounts for only 9.3 p.c. of that ingested. The small increase in the calcium excretion which remained is probably to be attributed to

the acidosis, as in the experiments of Givens and Mendel(10). The chloride figures show that 1.41 gram molecule above normal was excreted within 12 hours of the last salt being taken, out of 1.43 ingested, so the chloride must have been completely absorbed.

The negative balance of urinary phosphorus amounted to 85.8 millimols, or 2.66 grams on Oct. 21st, but taking the experiment as a whole it was only .37 gram, which may well be due to irregularity of the diet. There can therefore have been little increased loss of phosphorus in the fæces. It was impossible to collect these completely, but a stool of Oct. 19th contained 11.2 p.c. of solids, which gave off 71 c.c. of carbon dioxide at 0° and 760 mm. per gram on the addition of acid. This corresponds to a calcium carbonate content of 31.6 p.c. If all the fæcal phosphorus found was present as calcium phosphate ($\text{Ca}_3\text{P}_2\text{O}_8$), (and according to Rogozinski(11) about half of it is organic) the calcium phosphate only amounted to 9.3 p.c. of the dry weight. So at least 3.5 times as much calcium was being excreted in combination with carbonic as with phosphoric acid. A sample of normal fæces contained only .16 p.c. of calcium carbonate, even if all the combined carbon dioxide was in this form. No hydrogen sulphide was evolved on adding acid. There can be no doubt that calcium carbonate excretion was the main cause of the acidosis. In the neutral intestinal contents calcium carbonate was precipitated, bringing down the carbonate of the digestive juices and replacing it by chloride which was re-absorbed in accordance with the equation



Thus, as has been shown to be the case by Baird, Douglas, Haldane and Priestley(12) in ammonium chloride acidosis, the HCO'_3 of the plasma and tissues is partly replaced by Cl' , the alveolar carbon dioxide falling simultaneously so as to keep the cH of the blood approximately constant.

The alveolar carbon dioxide with a normal acid and ammonia excretion was 34–35 mm. as against 39–40 mm. in 1920, and 37–38 in the springs of 1922 and 1923. There was no evidence of kidney disease, and we are unable to account for the changes. The ammonia + acid excretion showed a roughly linear relation with the alveolar CO_2 as in 1920, but in this case the kidneys were somewhat more responsive, excreting as much acid + ammonia at low alveolar CO_2 pressures, and less at high ones.

Mr R. Webb, of the Pathological Laboratory, very kindly estimated

the hæmoglobin of the blood on Oct. 19, 20, and 23, and performed cell-counts on the first two dates. In addition, the hæmoglobin and cells were determined after the close of the experiment. The hæmoglobins were 12·5, 12·5 and 10 p.c. above normal, while the red blood corpuscles were increased by 10 and 8 p.c., the whites by 31 and 30 p.c., the increase in lymphocytes being especially marked. There was thus a concentration of the blood as found by Baird *et al.* (12) with ammonium chloride.

Calcium chloride has been successfully used by Blum (13) and his pupils in the treatment of dropsy, œdema and exudations. They find that large oral doses produce diuresis which may outlast the treatment for days, and great loss of sodium. The plasma proteins become more concentrated, and the weight falls. During calcium chloride ingestion in this experiment there was a large loss of water, partly by diarrhœa, and of sodium or potassium since the chloride excretion increased very much more than that of ammonia. Later there was retention of water, accompanied by thirst from Oct. 21st to 24th inclusive. There was also very great sodium or potassium retention, the ammonia excreted being sometimes enough to neutralize all the phosphoric and hydrochloric acids. Blum attributes the loss of sodium and water to antagonism between sodium and calcium, but this cannot be correct since the effect of ammonium chloride is precisely similar. In both cases HCO'_3 is replaced by Cl' in the blood and tissues. But so great is the loss of salt and water that the total amount of chlorine in the body remains unaltered. This appears from the urine analyses and also from the following observation. During a severe ammonium chloride acidosis 40 grams of sodium bicarbonate were eaten with water in two hours. This would normally cause diuresis and bicarbonate excretion. But neither took place nor did any extra chlorides appear in the urine. All this salt was therefore retained, the change of reaction making this possible.

A possible explanation of these phenomena is as follows. The reaction of the arterial plasma is kept nearly constant by the respiratory centre, but that of the tissues and capillary blood becomes more acid owing to loss of buffering power. For the excess of CO_2 pressure in the tissues over that in the blood, and the excess of CO_2 content of venous over arterial blood presumably remain unaltered, and therefore form larger proportions of the total CO_2 . The increase in hæmoglobin and other protein content is not enough to counteract this effect. The increased acidity brings the blood and tissue proteins nearer to their isoelectric points, and they therefore release cations which they are holding in

Donnan equilibrium, and diminish their osmotic pressure, thus losing water. If this view is correct, ammonium chloride or phosphate should prove a valuable alternative to calcium chloride where the latter is indicated as a diuretic.

SUMMARY.

1. Calcium chloride taken orally is mainly excreted in the fæces as calcium carbonate, the Cl' replacing HCO'_3 in the body and causing acidosis.

2. In calcium chloride and ammonium chloride acidosis the body loses water and salts.

3. Phosphates and ammonia account for less than half the buffering of normal urine between pH 3.7 and 9.0, but for more than half during acidosis.

TABLE.

Date Oct.	CaCl ₂ taken	Extra water drunk c.c.	Alv. CO ₂ mm. Hg.	Vol. c.c.	pH	NH ₃	Acid	Net acid	Phosphate	Buffers	Un-determined buffers	Ca	Cl
16	—	0	34.4	1005	6.4	24.2	34.2	31.3	19.9	61.2	37.4	2.8	162
16-17	—	—	—	455	5.9 -	22.2	36.9	33.3	19.9	55.0	31.5	1.7	39
17	225	1500	32.2	2815	5.6 -	78.0	56.3	33.8	24.8	71.5	34.2	10.4	443
17-18	—	—	—	1175	4.9	57.3	62.2	53.0	25.7	70.3	35.4	9.6	129
18	275	1000	30.3	1620	4.9	64.2	70.0	53.9	31.8	76.5	34.4	14.6	365
18-19	—	—	—	1450	5.0 -	99.9	85.7	69.7	34.7	88.3	37.6	16.5	333
19	275	1000	27.3	1475	4.9 +	102.4	85.7	69.3	36.1	91.5	39.0	16.2	363
19-20	—	—	—	1705	5.0 +	133.2	93.8	72.5	37.3	95.5	36.9	17.1	381
20	—	0	25.4	880	5.2 -	139.3	78.2	55.9	29.5	88.6	36.8	5.5	189
20-21	—	—	—	480	5.5 +	119.9	62.9	43.7	25.9	78.3	33.2	4.2	75
21	—	500	28.0	600	5.4	128.3	54.9	34.5	17.0	67.3	29.7	4.7	125
21-22	—	—	—	438	5.6 -	105.0	50.0	33.2	17.8	62.5	27.9	3.0	73
22	—	500	32.9	440	5.6	90.9	38.0	23.5	8.2	52.8	30.1	3.7	93
22-23	—	—	—	445	5.7 -	71.4	38.0	26.6	11.9	55.3	32.0	—	64
23	—	600	34.9	1082	5.9	70.1	31.2	20.0	6.3	47.1	29.6	—	105
23-24	—	—	—	561	6.0	42.1	30.6	23.9	14.6	48.9	27.6	—	81
24	—	400	35.0	1258	6.4 +	54.3	27.2	18.5	6.6	43.7	28.4	—	—
24-25	—	—	—	560	6.1	37.4	24.8	18.8	15.0	50.0	29.0	—	—
25	—	<i>ad lib.</i>	34.7	1980	6.4	49.9	28.5	20.5	6.8	61.2	46.4	—	—
25-26	—	—	—	502	—	25.0	26.3	22.3	19.2	47.8	24.6	—	—
26	—	<i>ad lib.</i>	33.9	2020	—	42.8	24.8	18.0	10.3	54.7	37.6	—	—
26-27	—	—	—	473	—	22.8	31.6	28.0	20.3	52.3	28.3	—	—
27	—	<i>ad lib.</i>	33.9	1464	—	31.7	21.8	16.7	12.3	54.6	37.3	—	—
27-28	—	—	—	472	—	—	—	—	19.6	—	—	—	—
28	—	<i>ad lib.</i>	—	2030	—	—	—	—	13.1	—	—	—	—
28-29	—	—	—	343	—	—	—	—	20.9	—	—	—	—

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