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HYPERTONIC DEHYDRATION AND SUMMER DIARRHOEA

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Diarrhoeal disorders are a major cause of morbidity and mortality in African children, especially during the summer months. Severe attacks occur mostly in children suffering from protein malnutrition.[1] Hypotonicity of the extracellular fluid occurs frequently in these dehydrated subjects.[2] Of the 1,000 children with diarrhoea and dehydration admitted to the paediatric wards of this hospital every year, 26·5% have serum-sodium levels of less than 125 mEq. per litre, while 60·5% have normal levels (126 – 144 mEq. per litre).

This leaves 13% who have serum-sodium levels of 145 mEq. per litre or more. These children are selected from a further 1,500 cases who receive intravenous therapy for dehydration in the out-patient department. Thus the actual incidence of hypertonic dehydration is probably 5 or 6% of the total number of infants and children attended for dehydration at this hospital. This form of dehydration has been reported with increasing frequency in recent years, particularly from the USA,[3-6] and its incidence, in dehydrated infants, ranges from 16 to 25%. In one series hypertonic dehydration was present in 17 (53%) of 32 children suffering from diarrhoea.[7] This high incidence was attributed to the oral administration of milk formulae high in solute content or to the use of oral aqueous solutions containing excessive amounts of electrolytes.[7] In this country Bowie *et al.*,[8] from Cape Town, reported an incidence of 34%.

In this paper we report 11 African children with hypertonic dehydration (5 of whom were briefly described previously[9]). It will be shown that neither excessive loss of water nor ingestion of concentrated saline solutions or milk formulae is likely to be the sole aetiological factor in the pathogenesis of this type of dehydration.

MATERIAL AND METHODS

The 11 children were selected, during a period of 3 months, from among 160 ward patients suffering from gastro-enteritis. A serum-sodium level of 145 mEq. per litre or more was the main criterion for inclusion in this series. This level was chosen in the light of two studies of normal serum-electrolyte levels carried out at this hospital. In one[10] the mean serum-sodium level was 136·3 (±4) mEq. per litre and in the other[11] 132·3 (±6) mEq. per litre. In the latter study the average serum-potassium level was 5·5 (±0·8) mEq. per litre, the average plasma-chloride level 98 (±7) mEq. per litre, and the average carbon-dioxide combining power 18·7 (±4) mEq. per litre. Blood-urea levels in normal controls were always less than 35 mg. per 100 ml.

The state of nutrition was assessed clinically. A child was considered to be malnourished if one or more of the following stigmata were found: (1) Patchy hypopigmentation or an acute nutritional dermatosis.[12] (2) Sparse straight hair with evidence of depigmentation. (3) Nutritional oedema. (4) A body weight below 40% of that expected for age; in the absence of normal weight standards for African children, we have compared the weights of our patients with those of normal American children.[13]

The degree of fluid loss was assessed by the difference between the patient's weight on admission and on discharge (the average stay in hospital was 9 days).

The following investigations were carried out on admission to hospital: Serum sodium and potassium were determined by means of an EEL flame photometer, plasma chlorides by the method of Schales and Schales,[14] carbon-dioxide combining power by the method of Van Slyke,[15] and blood urea by the urease method. Serum-salicylate levels were determined in 6 of the patients on admission. The urine was examined microscopically and for protein content and specific gravity, and in cases 9 and 10 the total urinary excretion of sodium, potassium and chloride was assessed over a period of 48 - 66 hours after commencement of therapy.

Treatment consisted of intravenous administration of 0·2% sodium chloride in 5% invert sugar (Na 34 mEq. per litre) in quantities of 80 - 100 ml. per lb. body-weight per 24 hours. Potassium chloride (27 mEq. per litre) was added to the intravenous infusion when the urinary output was adequate and provided that the serum-potassium level was not raised. Oral milk feeds were withheld until electrolyte levels returned to normal.

All patients received chloromycetin palmitate, 30 - 50 mg. per lb. body-weight per day, in divided doses. If there was an associated respiratory-tract infection, penicillin was administered in doses of 250,000 units by intramuscular injection every 6 hours.

CLINICAL AND BIOCHEMICAL FINDINGS

Some of the clinical and biochemical data of the 11 patients are summarized in Table I:

The age of the patients ranged from 2 to 10 months; 8 of them were males. The maximum rectal temperature exceeded 102°F (39°C) in 7 patients. In 7 patients the skin turgor was normal or only slightly impaired; in 3 there was a 'doughy' feel of the skin and subcutaneous tissues; in 1 (case 3) the skin was markedly inelastic. The state of nutrition was clinically good in 7 patients, fair in 2, and poor in 2, but none of the cases showed the features of kwashiorkor (protein malnutrition). Five patients weighed more than the average American child of the same age,[13] while only 2 were below the 3rd percentile.

In 9 of the 11 patients there were some neurological abnormalities such as irritability, stupor, tetany, coma or convulsions.

TABLE I. CLINICAL AND BIOCHEMICAL DETAILS OF 11 CHILDREN SUFFERING FROM HYPERTONIC DEHYDRATION

Case No.	Age (months) and Sex	Weight (1) On admission (2) On discharge (lb. and oz.) A	Degree of Dehydration B	Hyperpnoea C	Maximum Temperature °F	Skin Turgor D	Neurological Signs E	CSF Protein (mg. per 100 ml.) F	Respiratory System Involvement G	Clinical State of Nutrition H	Blood Electrolytes (mEq./litre) Na I	Cl J	K K	HCO_3 L	Blood Urea (mg./100 ml.) M	Serum Salicylate (mg./100 ml.) N	Haematocrit PCV% O	Haemoglobin (g./100 ml.) P	Urine S.G. Q	Urine Prot. R	Urine Casts S	Remarks
1	4 M	(1) 10, 12 (2) 11, 9	7	+	103	Sl. Imp.	Irr. HPC	—	Nil	G	156 132	142 100	4·8 3·6	6·7 16·2	74 13	—	34 35	12·0* 11·8†	1020	+++	Gran. (num.)	
2	10 F	(1) 22, 3 (2) 24, 1	8	+	106	Doughy	S. Coma. Hyp. Conv.	24	Nil	G	149 137 130	128 108 101	4·7 4·7 4·9	5·3 12·1 —	170 41 <10	—	41 31 34	13·5* 9·4† 10·7††	1008	++	Gran. (occ.)	
3	4 M	(1) 12, 14 (2) 14, 1	8	+	103	Poor	None	—	Creps. (*b*)	G	146 137	110 101	4·4 3·5	5·9 21·9	280 32	<5	32	10·4* †	—	++	Nil	Rickets
4	4 M	(1) 11, 14 (2) 10, 3‡	14‡	+	102·6	Normal	Irr. + MT Tet.	—	Br. pn. (*c*)	F	153 134 155	121 98 124	5·0 4·6 4·7	11·6 16·0 7·5	160 18 105	<5	 34 35	* † 11·0‡ 11·0†	—	Nil	Gran.	Rickets Relapse Died (Fig. 1)
5	5 M	(1) 12, 7 (2) 13, 12	10	+	105	Normal	Conv.	31	Br. pn. (*d*)	F	149 134	114 106	5·0 5·4	9·5 21·7	106 14	—	36 33	11·7* 10·2†	1008	+	Nil	Rickets
6	7 M	(1) 16, 2 (2) 17, 8	8	+	105	Sl. Imp.	Conv.	58	Creps. (*e*)	G	162 144	148 111	5·5 5·4	6·5 18·4	290 <10	<5	27	9·7* †	—	+++	Nil	Salmonella enteritis
7	4 F	(1) 12, 9 (2) 14, 13½	15	+	101	Sl. Imp.	Stup.	—	Nil	G	145 137 134	118 99 101	5·4 3·7 5·7	— 26·6 19·2	280 18 10	<5	29 30 30	10·5* 10·6† 10·6††	—	Trace	Nil	
8	6 F	(1) 12, 3 (2) 12, 14	5	+	105	Normal	Irr. Stup.	24 (*a*)	Nil	P	146 137	118 102	4·2 3·5	6·0 18·2	152 31		40 31	13·7* 10·9†		Trace	Not exd.	Table II
9	4½ M	(1) 13, 4 (2) 14, 8	9	+	100	Doughy	S. Stup.	—	Creps. (*f*)	G	150 134	126 106	3·1 5·0	5·0 18·6	182 17	<5	35 26	12·5* 8·3†	1020	+++	Hy and Gran.	Fig. 2
10	5½ M	(1) — (2) 11, 14	—	+	101	Normal	None	—	Otitis Media	P	156 130	114 99	3·8 6·0	4·5 19·7	76 57	<5	32 34	11·4* 11·6†	1007	+	—	Salmonella enteritis Rickets
11	2 M	(1) 8, 5 (2) 9, 3	10	+	100·5	Doughy	Drows.	—	Nil	G	148 134	106 98	4·7 —	8·7 17·9	103 20	—		* †				

Column A: ‡ During a relapse.
Column B: Based on column A, [(2)—(1)] ÷ (2) expressed as percentage. ‡ During a relapse.
Column C: + = Present.
Column D: Doughy = Doughy feel. Sl. Imp. = Slightly impaired.
Column E: Irr. = Irritable. Conv. = Convulsions. Stup. = Stuporose. Hyp. = Hypotonic. Tet. = Tetany. Drows. = Drowsiness. S. Stup. = Semi-stuporose. S. Coma. = Semi-comatose. HPC = High-pitched cry. + MT = Increased muscle tone.
Column F: CSF = Cerebrospinal fluid. Prot. = Protein. (*a*) Second specimen.
Column G: (*b*) Fine crepitations at right base. (*c*) Radiological evidence of bronchopneumonia. (*d*) Clinical and radiological bronchopneumonia left lower lobe. (*e*) Crepitations at both lung bases. (*f*) Crepitations right middle lobe.
Column H: G = Good. F = Fair. P = Poor
Columns I–P: * Before treatment. † After treatment. ‡ During a relapse. †† 2-3 months later.
Column Q: S.G. = Specific gravity.
Column R: Prot. = Protein.
Column S: Gran. = Granular. Hy = Hyaline. Not exd. = Not examined. Num. = Numerous. Occ. = Occasional.

Clinical or radiological evidence of acute respiratory disease was present in 6 of the 11 patients.

The degree of dehydration on admission was assessed at from 5 to 15% of the body-weight on discharge from hospital.

On admission to hospital the serum sodium ranged from 145 to 162 mEq. per litre and the plasma-chloride from 106–148 mEq. per litre. In 4 patients the serum-potassium was less than 4·7 mEq. per litre. The carbon-dioxide combining power was markedly lowered in all cases (4·5–11·6 mEq. per litre) and the blood-urea levels were always raised (74–290 mg. per100 ml.) The serum salicylate was always less than 5 mg. per 100 ml.

Serial haematocrit estimations were carried out in 8 cases, in 4 of whom there was significant fall during rehydration, while 4 remained unchanged.

In 3 of the cases there was a history of the infant's having received fluids high in solute content during the 24 hours before admission to hospital. Case 1 had received 1,200 ml. of a skimmed-milk mixture containing protein 3·93%, and Na 20, K 50, and Cl 40 mEq. per litre. Case 3 had been given orally 900 ml. of M/6 sodium lactate (Na 167 mEq. per litre) and 1,000 ml. of a skimmed-milk formula. Case 11 had received 150 ml. of intravenous M/6 sodium lactate and been fed with 400 ml. of a half-cream milk mixture.

Only 1 of the 11 children died (case 4). The findings at the autopsy were as follows: Areas of bronchopneumonia in both lungs. Patchy mucosal congestion of the intestine. The kidneys, apart from some congestion, showed no lesions either macroscopically or microscopically. The brain and intracranial venous sinuses were macroscopically normal. Section of a costochondral junction showed evidence of rickets. Fig 1 shows the serial biochemical, haematocrit and weight changes in this case.

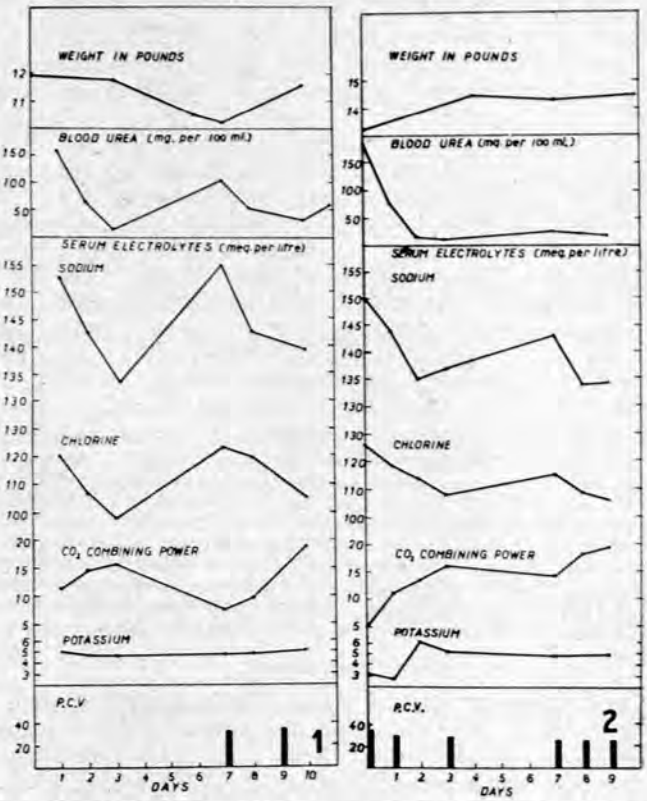

Fig. 1. Serial changes in body-weight, blood electrolytes and haematocrit in case 4 until death on the 11th day. (Note the relapse on Day 7.)

Fig. 2. Serial changes in body weight, blood electrolytes and haematocrit in case 9 throughout stay in hospital. (Note the mild relapse on the 7th day.)

CASE REPORTS

Case 8

In this case we were able to observe the sequence of events which led to the development of hypertonic dehydration. The child was admitted with a 3-day history of diarrhoea and vomiting and a 2-day history of cough and rapid respiration. There was no history that excessive saline or concentrated milk-powder mixtures had been given. On examination the patient was hyperpnoeic, with normal skin turgor and a rectal temperature of 105·5°F (40·8°C). Electrolyte estimations showed a sodium level of 135 mEq. per litre with a raised chloride level of 113 mEq. per litre and a low carbon-dioxide combining power (Table II). During the first 10 hours the child refused some of the milk feeds and vomited the others. No stools were passed and only one wet napkin was noted. The child then became comatose and remained hyperpnoeic, the eyes became sunken, and the rectal temperature remained high (104·5°F—40·3°C). Serum-electrolyte estimations repeated 10 hours after admission showed that the serum sodium had risen to 146 mEq. per litre and the plasma chloride to 118 mEq. per litre.

TABLE II. CASE 8. BLOOD STUDIES

	Electrolytes (a)				*Urea (b)*	*Haemo-globin (c)*	*Packed Cell Volume*
	Na	*K*	*HCO_3*	*Cl*			
On adm. ..	135	3·8	6·8	113	109	14·0	40%
10 hrs. ..	146	4·2	6·0	118	152	13·7	40%
2 days ..	137	3·5	18·2	102	31	10·9	31%

(*a*) mEq./litre. (*b*) mg./100ml. (*c*) g./100ml.

With routine treatment of the hypertonic dehydration, the serum electrolyte levels returned to normal by 48 hours after admission, coincidentally with clinical improvement.

Case 9

This patient was anuric for 29½ hours. When urinary output was re-established, the excretion of sodium, potassium and chloride was estimated in the urine for a period of 66 hours after commencement of treatment (Table III).

The patient, a breast-fed boy, aged 4½ months, was admitted with a history of diarrhoea for 7 days and a cough for 2 days. There was no history of ingestion of electrolyte solution. Two days before admission the infant began to breathe rapidly, and was very hot and sleepy. No urine had been passed for 24 hours.

Physical examination revealed a fairly well nourished child with marked hyperpnoea and a rectal temperature of 100°F (37·7°C). The eyes were sunken but the skin and subcutaneous tissues over the anterior abdominal wall had a doughy feel. There were crepitations audible over the right middle lobe.

Fig. 2 shows the changes in body weight, blood electrolytes and packed cell volume throughout his stay in hospital.

The patient began to pass urine 5½ hours after commencement of intravenous therapy. The first period of urine collection lasted for 42 hours. The volume passed was 750 ml. containing, per litre, sodium 48 mEq., potassium 10 mEq., and chloride 48 mEq. During the same period a total of 2,300 ml. of fluid was administered containing, in all, 59 mEq. of sodium, 34 mEq. of potassium, 68 mEq. of chloride and 25 mEq. of lactate. Urine was collected for a further 24 hours (volume 900 ml. containing, per litre, sodium 2·9 mEq., potassium 3·3 mEq., and chloride 20 m.Eq.), during which period a total of 1,900 ml. of fluid was administered containing, in all, sodium *nil*, potassium 13·5 mEq. and chloride 13·5 mEq. During the 66-hour period of rehydration the serum sodium fell from 150 to 135 m.Eq. per litre and the serum chloride from 126 to 114 mEq. per litre; while the serum potassium rose from 3·1 to 6·1 mEq. per litre.

TABLE III. CASES 9 AND 10. URINE ELECTROLYTE EXCRETIONS COMPARED WITH SERUM ELECTROLYTE CONCENTRATIONS AND FLUID INTAKE

	Serum			*Intake*				*Urine*			
	Na	*K*	*Cl*	*Vol.*	*Na*	*K*	*Cl*	*Vol.*	*Na*	*K*	*Cl*
		mEq./litre		*ml.*		*mEq.*		*ml.*		*mEq./litre*	
Case 9											
First 42 hours	144	2·7	118	2,300	59	34	68	760	48	10	48
Next 24 hours	135	6·1	114	1,900	Nil	13·5	13·5	900	2·9	3·3	20
Case 10											
First 16 hours	156	3·8	114	900	25	Nil	17	184	22	5·6	31
Next 24 hours	140	3·1	108	1,500	34	33·7	67·7	750	23	2·4	57

This patient had a mild relapse of hypertonic dehydration on the 7th hospital day caused by refusal of feeds and increased frequency of stools.

Case 10

This patient was anuric for 8 hours. Urine collected for the first 16 hours after starting treatment showed a volume (Table III) of 184 ml. containing, per litre, sodium 22 mEq., potassium 5·6 mEq. and chloride 31 mEq. The total fluid given during this period was 900 ml. containing, in all, sodium 25 mEq., lactate 8 mEq. and chloride 17 mEq. The subsequent 24-hour urine volume was 750 ml. containing, per litre, sodium 23 mEq., potassium 2·4 mEq. and chloride 57 mEq., while the amount of fluid administered during this latter period was 1,500 ml., containing, in all, sodium 34 mEq., potassium 33·7 mEq. and chloride 67·7 mEq.

DISCUSSION

The majority of previous reports have considered a serum-sodium level of 150 mEq. per litre as biochemical evidence of hypertonic dehydration. In this series, patients have been included with serum-sodium levels above 145 mEq. per litre because in several investigations at this hospital[10,11] the normal sodium values have been found to be at least 5 mEq. lower than elsewhere.

Aetiology and Pathogenesis of Hypertonic Dehydration

Balance studies[4,5] have shown fairly conclusively that water is lost in excess of sodium in hypertonic dehydration. This water deficit has been ascribed to one or more of the following factors:

1. Diarrhoeal stools of low electrolyte content.
2. Deficient water intake.
3. Increased insensible water loss, i.e. *via* lungs and skin, brought about by high fever and/or hyperpnoea[16,17] and accentuated by metabolic acidosis.
4. Ingestion of electrolyte solutions or milk feeds high in solute content.[7]

What part did the aforementioned factors play in this series of cases?

1. All of our patients suffered from diarrhoea but we were unable to determine the water and electrolyte content of the stools, and therefore could not assess the exact part played by this factor. Other authors[5,18] have found a wide variation in the electrolyte concentrations of infant diarrhoeal stools. We therefore cannot exclude the possibility of a relatively greater loss of water than of electrolyte in the stools of our infants.

2. A definite history of restricted fluid intake for some hours before admission was obtained in 4 of the cases.

3. All our patients had deep and rapid respirations (hyperpnoea) and this must have contributed materially to the water loss. In contrast, Weil and Wallace[5] noted hyperpnoea in only one of their cases with hypertonic dehydration. Because of the marked acidotic respiration with little or no signs of clinical dehydration, salicylate intoxication was considered in the differential diagnosis, but serum-salicylate levels, where estimated, were found not to be raised.

A combination of high fever and metabolic acidosis was probably responsible for the hyperpnoea in our cases. Rectal temperatures of over 102°F (39°C) were found in 7 of the 11 infants. Respiratory infection, in addition to the gastro-enteritis, may have contributed to the high temperatures and also to the hyperpnoea in 6 of the 11 cases. It is noteworthy that Finberg *et al.*[4] reported 8 cases of hypernatraemia with respiratory infection who had no diarrhoea.

Weil and Wallace[5] found a lowered blood pH in infants with hypertonic dehydration, indicating a metabolic acidosis. They also observed that plasma-chloride levels were raised relatively more than the corresponding serum-sodium levels. We have confirmed the latter observation in our patients. The hyperchloraemic acidosis results in increased rate and depth of respiration with further water loss from the lungs and establishes a vicious cycle of hyperpnoea → water loss → hyperelectrolytaemia → metabolic (hyperchloraemic) acidosis → hyperpnoea, etc.

Case 8 demonstrated well the genesis of hypertonic dehydration. The deterioration during the 10-hour period of observation could be attributed to gross hyperpnoea, high body temperature and diminished fluid intake with resultant loss of water but negligible electrolyte loss.

4. Concentrated sodium-chloride solutions or milk formulae high in solute content given during the course of diarrhoea sometimes cause hypertonic dehydration,[5,7] but this factor operated in only 3 of our cases.

The Renal Factor

The metabolic acidosis as well as the hyperelectrolytaemia are aggravated by the renal response of the infant to water deprivation. Calcagno and Rubin[19] found that in infants deprived of water there was a marked reduction in the glomerular filtration rate (GFR) and a greater tubular reabsorption of filtered sodium and chloride, with a resultant elevation of serum sodium and chloride and a low electrolyte content of the urine.[5] This contrasts with the adult undergoing water deprivation, in whom there is a normal renal plasma flow[20] and a minimal reduction of GFR.

All our patients had a markedly raised blood urea. This taken in conjunction with the frequently observed oliguria or anuria must indicate considerable reduction in the GFR.

The initial oliguria or anuria in these patients suggests that the renal lesion may be acute tubular necrosis. Against this view is the low output of electrolytes in the presence of

adequate urinary volume that was observed during the recovery phase of cases 9 and 10. There is usually a large loss of electrolytes during the diuretic phase of patients recovering from renal tubular necrosis.[21]

The Nutritional Status of our Cases

The most striking feature in this series was the good state of nutrition of the patients, 7 of them still being breast fed. Of the 11 patients, only 2 were markedly below the average weight in relation to age.[13] Furthermore, none showed any stigmata of malnutrition. Thus 81% of these children were reasonably well nourished. This contrasts with the fact that the majority (85%) of patients suffering from gastro-enteritis admitted to our wards show evidence of poor nutrition.

This factor of good nutrition in our patients assisted us in the diagnosis of hypertonic dehydration. We suspected the condition if a child with a history of diarrhoea showed marked hyperpnoea and minimal clinical signs of dehydration, and was well nourished. Nervous symptoms or signs with a high rectal temperature were the principal additional features which strengthened clinical suspicion of hypertonic dehydration.

Children suffering from malnutrition and dehydration usually have serum-sodium levels below 130 mEq. per litre, and extremely rarely is a level of 140 mEq. per litre exceeded.[22] The 11 patients reported here all had serum-sodium levels of 145 mEq. per litre or more. Thus it appears that there is some fundamental difference in the response to diarrhoea between well nourished children and malnourished infants.

Studies on the intracellular and extracellular composition of fluids in malnourished children[2,23-25] have demonstrated that even in the presence of dehydration, the water content of the cells and of the extracellular fluid is increased when compared with well nourished infants. The injection of hypertonic saline solution restores to normal the abnormal electrolyte content of the malnourished child and benefits the clinical condition. From this it follows that factors leading to hypertonicity in well nourished children will cause a return to normality in the malnourished child. This may account for our failure to find cases of hypertonic dehydration among malnourished children.

The prognosis of gastro-enteritis is better if the child is well nourished than if it is malnourished. Hypertonic dehydration, however, constitutes a serious threat even to the well noursished group as shown by comparative mortality figures of other authors.[4] In our series the mortality was low.

SUMMARY

1. The clinical and biochemical features of 11 African children with hypertonic dehydration associated with summer diarrhoea are presented. There was one death in this series and brief mention is made of the autopsy findings in this case.

2. The factors which may have contributed to the development of hypertonic dehydration in our patients are considered.

3. The pattern of electrolyte and water excretion in the urine was studied in 2 patients for periods of 40 and 66 hours after commencement of therapy.

4. This series of infants were relatively well nourished, which was in striking contrast to the majority of infants with gastro-enteritis admitted to Baragwanath Hospital, who are poorly nourished and often develop hypotonic dehydration. An explanation for the difference in response between these children and the well nourished infants, who developed hypertonic dehydration, is suggested by recent work done on the intracellular and extracellular composition of malnourished infants suffering from dehydration.

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REFERENCES

1. Kahn, E. (1957): S. Afr. Med. J., **31**, 47.
2. Gomez, F., Ramos-Galván, R., Cravioto, J., Frenk, S., Janeway, C., Gamble, J. L. and Metcoff, J. (1957): Pediatrics, **20**, 101.
3. Rapoport, S. (1947): Amer. J. Dis. Child., **74**, 682.
4. Finberg, L. and Harrison, H. E. (1955): Pediatrics, **16**, 1.
5. Weil, W. B. and Wallace, W. M. (1956): *Ibid.*, **17**, 171.
6. Skinner, A. L. and Moll, F. C. (1956): Amer. J. Dis. Child., **92**, 562.
7. Colle, E., Ayoub, E. and Raile, R. (1958): Pediatrics, **22**, 5.
8. Bowie, M. D., McKenzie, D. and Hansen, J. D. L. (1958): S. Afr. Med. J., **32**, 322.
9. Slone, D., Levin, S. E. and Orska, I. (1958): Med. Proc., **4**, 265.
10. Politzer, W. M. and Wayburne, S. (1957): Brit. J. Nutr., **11**, 105.
11. Levin, S. E.: Unpublished data.
12. Trowell, H. C., Davies, J. N. P. and Dean, R. F. A. (1954): *Kwashiorkor*, p. 83. London: Arnold.
13. Nelson, W. E. (1950): *Text-book of Pediatrics*, p. 54. Philadelphia: W. B. Saunders Co.
14. Schales, O. and Schales, S. (1941): Biol. Chem., **140**, 879.
15. Peters, J. P. and Van Slyke, D. D. (1932): *Quantitative Clinical Chemistry*, vol. 2, p. 244. Baltimore: Williams and Wilkins
16. Heeley, A. M. and Talbot, N. B. (1955): Amer. J. Dis. Child., **90**, 251.
17. Finberg, L. (1958): Pediatrics, **22**, 2.
18. Holt, L. E., Courtney, A. M. and Fales, H. L. (1915): Amer. J. Dis. Child., **9**, 213.
19. Calcagno, P. L. and Rubin, M. I. (1951): Pediatrics, **7**, 328.
20. Wright, S. (1952): *Applied Physiology*, p. 67. London: Oxford University Press.
21. Bull, G. M., Joekes, A. M. and Lowe, K. G. (1950): Clin. Sci., **9**, 379.
22. Kahn, E. (1959): Amer. J. Clin. Nutr., **7**, 161.
23. Frenk, S., Metcoff, J., Gomez, F., Ramos-Galván, R., Cravioto, J. and Antonowicz, I. (1957): Pediatrics, **20**, 105.
24. Gordillo, G., Soto, R., Metcoff, J., Lopez, E. and Antillon, L. G. (1957): *Ibid.*, **20**, 303.
25. Metcoff, J., Frenk, S., Gordillo, G., Gomez, F., Ramos-Galván, R., Cravioto, J., Janeway, C. A. and Gamble, J. L. (1957): *Ibid.*, **20**, 317.