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Congenital chloride diarrhoea

Clinical analysis of 21 Finnish patients

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SUMMARY Clinical findings in 21 Finnish children with congenital chloride diarrhoea are reported. Inheritance of this disease by the autosomal recessive mode is established. All children were born 1–8 weeks prematurely. Hydramnios was present in every case and no meconium was observed; intrauterine onset of diarrhoea is thus apparent. In most cases the diarrhoea or passing of large volumes of 'urine' was noted on the first day of life and the abdomen was usually large and distended. The neonatal weight loss was abnormally large, and was associated with hypochloraemia and hyponatraemia. Some infants survived the neonatal period without adequate therapy. They presented later with failure to thrive and usually had hypochloraemia, hypokalaemia, and metabolic alkalosis associated with hyperaldosteronism. However, these features may be absent and the diagnosis is based on a history of hydramnios and diarrhoea, and a faecal Cl^- concentration which always exceeds 90 mmol/l when fluid and electrolyte deficits have been corrected. Lower faecal Cl^- concentrations were seen only in chronic hypochloraemia, which is also associated with achlorihuria.

Adequate treatment consists of full continuous replacement of the faecal losses of water, NaCl, and KCl. This should be given intravenously in the early neonatal period; later a solution can be taken orally with meals. The dose has to be adjusted to maintain normal serum electrolyte concentrations, normal blood *p*H, and some chloriduria. This therapy prevents the renal lesions and the retarded growth and psychomotor development which were seen in the children who were diagnosed late and in those who received inadequate replacement therapy. The watery diarrhoea persists and increases slightly with age, though patients learn to live with their disease and to make an adequate social adjustment.

In 1945 Gamble *et al.* and Darrow both described a child who had persistent watery diarrhoea, a high faecal concentration of Cl^-, hypochloraemia, hypokalaemia, and metabolic alkalosis, and they diagnosed the illness as 'congenital alkalosis with diarrhoea'. Since then 19 more cases have been reported from outside Finland: from the United States (Kelsey, 1954; Owen, 1964; Tucker *et al.*, 1964; McReynolds, *et al.*, 1974); the Netherlands (Duyck, 1955); the United Kingdom (Evanson and Stanbury, 1965; Harries, 1969; Davidson *et al.*, 1972; Lee and Harries, 1973; Pearson *et al.*, 1973); France (Harteman, 1966; Chaptal *et al.*, 1967; Lauras *et al.*, 1973); Denmark (Yssing and Friis-Hansen, 1966); Japan (Yanagisawa, *et al.*, 1968); Belgium (Loeb *et al.*, 1970); Norway (Michalsen, 1972); Poland (Hager-Malecka *et al.*, 1973); and Germany (Bremer and Heinisch, 1973).

In Finland this disease, which we prefer to call congenital chloride diarrhoea (CCD), was diagnosed for the first time in 1960, and since then an average of 2 new cases have been diagnosed annually (Perheentupa *et al.*, 1965; Launiala *et al.*, 1968; Norio *et al.*, 1971). We have now treated 21 children with CCD; 3 have died.

CCD is inherited as an autosomal recessive trait, which implies an abnormality in a single gene pair, a single protein, and a single cell function (Norio *et al.*, 1971). Launiala *et al.*, (1968) showed that the intestinal defect is located in the distal ileum and colon. Studies of the ileum (Turnberg, 1971; Bieberdorf *et al.*, 1972; Pearson *et al.*, 1973) and colon (Lauras *et al.*, 1973; Pearson *et al.*, 1973; Holmberg *et al.*, 1975) have shown, moreover, that this defect is impaired active Cl^- absorption probably resulting from an absence or impairment of the

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Cl^-/HCO_3^- exchange mechanism in these segments of the intestine. Cl^- is lost into the stools and osmotic diarrhoea develops. The absence of HCO_3^- causes the intestinal contents to become acid which in turn restricts the absorption of Na^+. Secretion of K^+ is increased (Holmberg, *et al.*, 1975).

This paper describes the Finnish CCD patients, their clinical picture, their physical and psychomotor development, and our method of treatment. The pathophysiology and the renal lesion will be discussed in detail elsewhere (Holmberg, 1977; Holmberg *et al.*, 1977).

Antenatal manifestations

Fetal diarrhoea. Hydramnios (2–6 l) always heralded the birth of a child with CCD. This suggests that the diarrhoea begins *in utero*. Further evidence of this is the lack of meconium noted in 14 infants carefully observed on the first day of life. All these infants had diarrhoea from birth. In the amniotic fluid of 2 patients the concentration of Na^+ was 126 mmol/l (126 mEq/l) in both, K^+ 3·4 and 4·4 mmol/l (3·4, 4·4 mEq/l), and Cl^- 102 and 108 mmol/l (102, 108 mEq/l), respectively. In the first of these infants serum electrolyte concentrations at 2 hours were Na^+ 105, K^+ 4·0, and Cl^- 81 mmol/l, and the faecal concentration of Cl^- at 24 hours 134 mmol/l. Electrolyte concentrations in the amniotic fluid in CCD are therefore normal. CCD should be considered in cases of hydramnios, especially in a woman who has had previous hydramnios resulting in perinatal death. CCD cannot be verified through amniocentesis.

Length of gestation. All 21 infants were born before term and 19 by 2 weeks or more (Table 1). Prematurity is presumably a consequence of the hydramnios.

Fetal growth. The lengths and weights at birth are shown in Fig. 1. The mean length was normal for the duration of gestation. The mean weight was slightly higher, probably owing to the intestinal accumulation of water. Most infants were born with a distended abdomen.

Neonatal manifestations

Diarrhoea. In 14 patients diarrhoea and an absence of meconium were noticed on the first day of life. Diarrhoea often goes unnoticed because the fluid in the diaper is thought to be urine. In fact, several patients in whom diarrhoea was not observed were reported to have passed large volumes of urine. On the first day of life about 150 ml fluid was lost with the stools. The Cl^- concentration in this fluid was 100–150, usually about 130 mmol/l. During the first 3 months of life the sum of the concentrations of Na^+ and K^+ usually exceeded the concentration of Cl^- (Fig. 2). This is in contrast to the situation which has been observed regularly beyond age 3 months. Stool *p*H was between 4 and 6.

Table 1 *Neonatal characteristics of 21 patients with congenital chloride diarrhoea (CCD)*

Patient	*Duration of gestation (w)*	*Age diarrhoea noticed*	*Bilirubinaemia* (mg/100 ml)*	*Distended abdomen*	*Neonatal weight loss (% of birthweight)*	*Age CCD diagnosed*
RK	34	3 w			20·2	
MK	37	1 d	23·3‡		14·2	5 d
RKo	34	4 m	27·0†	+	19·5	8 m
AS	34	1 d	29·9	+	26·6	9 m
RJ	34	1 d	24·2	+	12·7	4 m
JT	34	1 d	30·0§	+	27·2	2 m
LI	36	6 m			18·0	14 m
PI	39	1 d	15·0		14·4	3 d
JH	38	3 w			23·9	3 w
MH	34	1 d	26·0†	+	16·7	1 d
J-PK	37	1 d	24·6	+	26·9	3 d
MV	37	3 m			n.d.	4 m
RV	34	1 d	18·4	+	11·0	1 d
MKu	33	1 d	21·0	+	23·9	1 d
SA	34	1 d	22·0	+	20·5	1 d
AT	35	3 w	21·0†	+	15·8	25 m
KR	36	1 d	18·0	+	22·4	2 m
HP	36	1 w	23·0	+	26·5	2 m
TR	35	1 d	17·2	+	15·3	1 d
JK	36	1 d	12·3	+	12·6	1 d
A-JS	32	1 d	20·0	+	17·8	1 d

*Highest concentration measured. Blood group incompatibility present: †A, ‡B, §D. *Conversion: Traditional units to SI*—Bilirubin: 1 mg/100 ml $\approx$17·1 μmol/l.

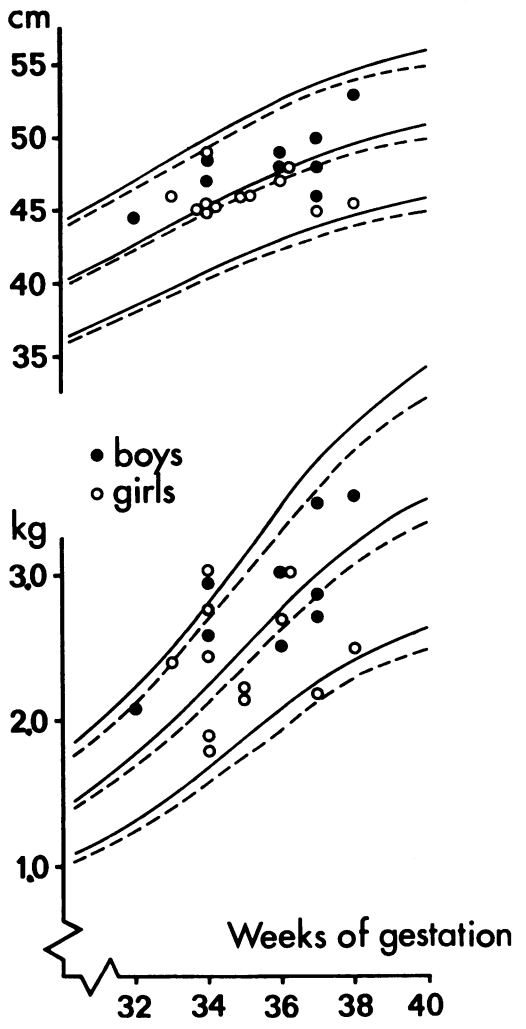

Fig. 1 *Birth lengths and weights of 21 children with CCD. The lines indicate normal mean±2·5 SD.* —— *boys;* — — — *girls.*

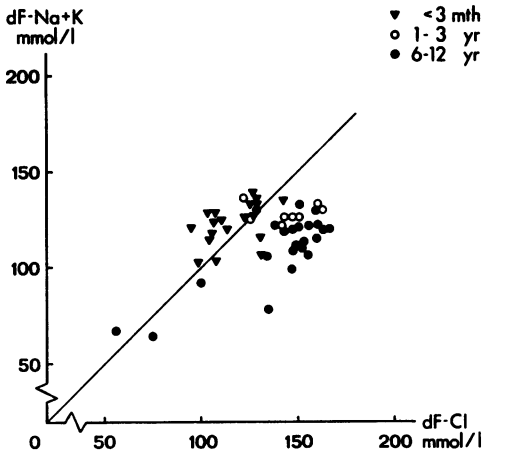

Fig. 2 *Relationship of the sum of the concentrations of Na^+ and K^+ to the concentration of Cl^- in the faeces (dF) of CCD patients at different ages.* Conversion: SI to traditional units—*Electrolytes :1 mmol/l = 1mEq/l.*

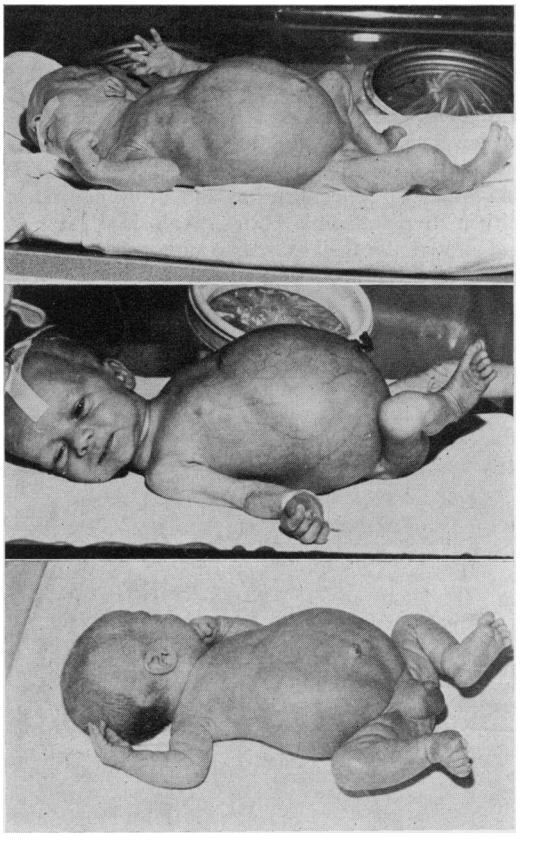

Fig. 3 *Appearance of 3 newborn CCD patients.*

Abdominal distension. The abdomen was usually large and distended (Fig. 3) and was often the reason for admission to hospital. Movements of the bowel were visible. Several patients were suspected of having an intestinal occlusion and an aganglionic segment. *X*-rays showed that loops of ileum and colon were dilated with air and fluid (Fig. 4). In all but one infant this state of paralytic ileus lasted several weeks, finally subsiding on conservative therapy. In patient TR a volvulus developed at 8 weeks. This complication has been reported in 3 other CCD patients (Tucker *et al.*, 1964; Lee and Harries, 1973; Pearson *et al.*, 1973). A constant

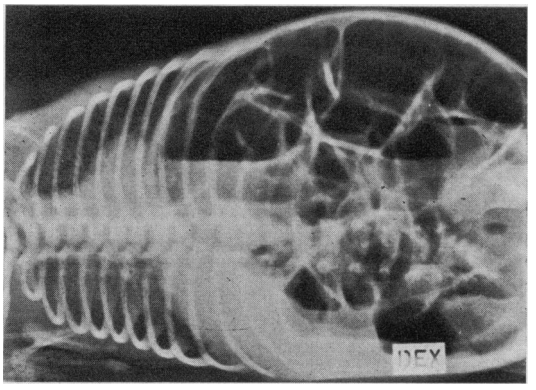

Fig. 4 *X-ray of the distended abdomen of a newborn CCD patient. Intestinal loops are dilated with fluid and air and a hydroperitoneum is present.*

voluminous filling of intestinal loops probably creates a predisposition to a volvulus.

Total exchangeable K^+ estimated in two 4-week-old patients whose abdomens continued to be severely distended was 32·2 and 34·3 mmol/kg, respectively, slightly below normal (38–46 mmol/kg). Such a mild K^+ depletion is unlikely to cause intestinal atonia.

Water, electrolyte, and acid-base status. Because CCD was suspected in patient RV at birth serum electrolyte and *p*H status were determined at 1 hour. Na^+ and Cl^- concentrations were low but he had neither hypokalaemia nor alkalosis (Table 2). In 5 others serum electrolyte concentrations were measured 20–30 hours after birth but before weight loss, by then about 7·7–13·0% of birthweight, had been replaced. All concentrations were normal. In 6 others these values were first recorded, also before treatment, at the age of 7 days. Most patients had clear hyponatraemia and hypochloraemia (Table 2), whereas only 2 had low concentrations of K^+. Fig. 5 shows that the neonates reacted to the fluid loss with a hypo-osmolality associated with hyponatraemia, hypochloraemia, and a slight rise in HCO_3^- concentrations.

The inability to maintain a normal concentration of Na^+ in the first weeks of life suggests an immaturity of the aldosterone system. Because excretion of *p*H 1 hydrolysable aldosterone (Bayard *et al.*, 1970) was 2·3 $\mu g/m^2$ per 24 h in the first day in patient RV and 7·6 $\mu g/m^2$ per 24 h on the third day in JK, aldosterone production did not seem to be impaired in the newborn (normal range 2–12 $\mu g/m^2$ per 24 h). At the age of 7 days only one child was alkalotic, the others were clearly acidotic. Thus although the diarrhoea of CCD is congenital, the alkalosis is not, and the original name of this disease, 'congenital alkalosis with diarrhoea' is a misnomer. If sufficient replacement therapy was not started during the first weeks, severe alkalosis developed and the plasma concentrations of Cl^-, K^+, and Na^+ fell, the lowest values in our patients being *p*H 7·68 and electrolytes 54, 1·7, and 107 mmol/l respectively.

Most patients will probably not survive if adequate replacement therapy is not provided at this stage. 7 of the previous infant deaths in the 18 families we studied were probably due to CCD. These infants were born prematurely after hydramnios and died in the first months of life with distended abdo-

Table 2 *Serum (blood) electrolyte concentrations (mmol/l) and pH before diagnosis and treatment*

Patient	*Age*	*Weight loss (% of birthweight)*	*Serum*			*Blood*		
			Na^+	*K^+*	*Cl^-*	*pH*	*Standard bicarbonate*	*Base excess*
RV	1 h	ND	105	4·0	81	7·24	19·1	−6·6
MH	1 d	8·3	148	4·3	109	ND	ND	ND
MKu	1 d	9·6	148	7·9	117	7·42	22·0	−2·4
SA	1 d	10·5	148	7·2	96	7·28	18·7	−7·7
TR	1 d	13·0	144	5·5	108	ND	ND	ND
A-JS	1 d	7·7	133	5·2	97	7·34	21·5	−3·6
RK	7 d	19·5	123	2·6	83	7·34	20·3	−4·1
JT	7 d	27·2	122	2·4	72	7·42	20·8	−4·0
MH	7 d	22·3	110	5·6	76	7·39	21·2	−3·5
J-PK	7 d	20·8	128	4·0	68	7·42	30·5	+8·8
MK	7 d	23·9	127	3·5	88	ND	ND	ND
SA	7 d	20·5	124	3·7	87	ND	ND	ND
RJ	16 w	ND	128	3·3	80	7·39	35·0	+12·0
MV	18 w	,,	134	2·8	57	7·68	40·0	+18·0
LI	14 m	,,	133	2·6	85	7·51	28·0	+5·0
AT	24 m	,,	137	3·7	80	7·52	32·0	+10·1

*ND = not determined. *Conversion: SI to traditional units*—Electrolytes: 1 mmol/l = 1 mEq/l.

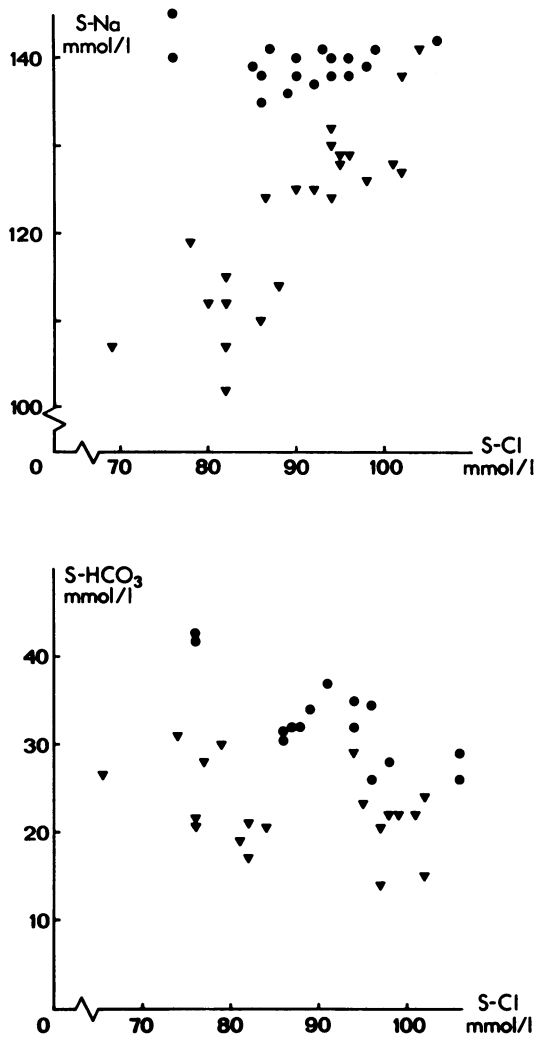

Fig. 5 *Relationship of (S) serum Na^+ and serum HCO_3^- concentrations to the serum Cl^- concentration in newborn (▼ =<1 m) and older (●=>1 m) CCD patients.*

men and diarrhoea. There were other early deaths in these families in unknown circumstances; such cases have been labelled as 'possible CCD' in Table 3. Patient MKu died at 19 days of age because intravenous replacement of existing deficits was insufficient. Infants in whom intravenous replacement of water and electrolytes was adequate from the first day of life remained free of electrolyte and *p*H disturbances and had continuous chloriduria (Table 4).

Jaundice. Most patients had hyperbilirubinaemia. 7 patients required one or more exchange transfusions and of these 5 had a known blood group incompatibility (Table 1). While prematurity, acidosis, and dehydration evidently contributed to the hyperbilirubinaemia, they were not constantly severe and it appears that in CCD some additional factor may be involved.

Table 3 *Finnish CCD sibships*

Patients	*Year of birth*	*Sibship*
RK & MK	1960, 1961	■ ■
RKo	1963	(○) ⊗ ◪ ● ○
AS	1963	□ ● ○
RJ	1964	●
JT	1964	□ ●
LI & PI	1964, 1966	● ● □
JH	1965	○ ○ ◔ ○ ◔ ○ ○ □ □ ○ ■
MH	1966	○ ●
J-PK	1966	◔ □ ■ □
MV & RV	1967, 1973	■ ◪ ■
MKu	1969	□ □ ⊗ □ □ ●
SA	1970	○ ⊗ ○ □ ○ ■
AT	1971	● ○
KR	1971	●
HP	1971	◪ □ ○ ■
TR	1972	●
JK	1974	◔ ■
A-JS	1974	■

Key to the symbols: ● ■ evident CCD, ◔ ◪ probable CCD, ⊗ ⊠ possible CCD

Diagnosis. In the newborn the diagnosis is established when there is hydramnios and watery diarrhoea in which the faecal concentration of Cl^- exceeds 90 mmol/l. A stool sample is easily obtained from the rectum with a soft catheter.

Later manifestations; with no treatment

A few CCD infants will survive the first months without adequate replacement therapy. In most patients reported from other countries and in 4 of our own (Table 1) the diagnosis was not made until they were between 6 months and 2·5 years old.

Diarrhoea. Of our late diagnosed children RJ was admitted to hospital aged 2 days for hyperbilirubinaemia and pneumonia and discharged 6 weeks later. 'Soft stools' were noticed during this period. At home neither she nor patient AT were ever known to pass a formed stool. Diarrhoea in MV was first noticed in a nursery in which he was placed when 3 month old. The mother of LI noticed soft stools at the age of 6 months and later watery diarrhoea. In all these patients the characteristically high faecal concentration of Cl^- was subsequently shown.

Urine. All children in whom the diagnosis was made after the age of 6 months had Cl^--free urine, which has been considered characteristic of CCD. Fig. 6 shows, however, that the presence or absence of

Table 4 *Electrolyte concentrations (mmol/l), and pH in serum (blood), and 24-hour volumes (ml) of urine and faeces in patient RV*

Age	*Weight (g)*	*Serum*			*Blood*			*Urine*					*Faeces*				
		Na^+	*K^+*	*Cl^-*	*pH*	*Standard bicarbonate*	*Base excess*	*Volume*	*pH*	*Na^+*	*K^+*	*Cl^-*	*Volume*	*pH*	*Na^+*	*K^+*	*Cl^-*
2 d	2870	136	4·2	112	7·36	22	−3·0	110	7·5	15	7	9	165	5·7	133	12	145
14 d	2750	144	5·6	116	7·35	21	−4·1	285	5·0	8	13	23	120	5·3	71	31	99
25 d	3020	138	4·4	107	7·38	19	−5·9	240	5·4	4	12	15	170	5·2	76	44	114
39 d	3600	144	4·5	108	7·41	26	+1·4	290	6·0	10	24	14	105	5·5	56	79	143
22 w	7930	138	4·9	112	7·40	23	−1·7	355	6·9	62	88	25	280	5·2	61	53	158
12 m	11000	143	4·7	115	7·38	20	−5·1	450	6·8	115	57	95	500	4·9	82	47	145

During first month treatment was 150 mmol Cl^-/m^2 per 24 h (Na^+/K^+ =9/1 to 3/1). Thereafter a 0·7% NaCl—0·3% KCl solution was given in doses gradually reduced from 90 mmol/m^2 per 24 h at 1 month to 75 mmol/m^2 per 24 h at 12 months.

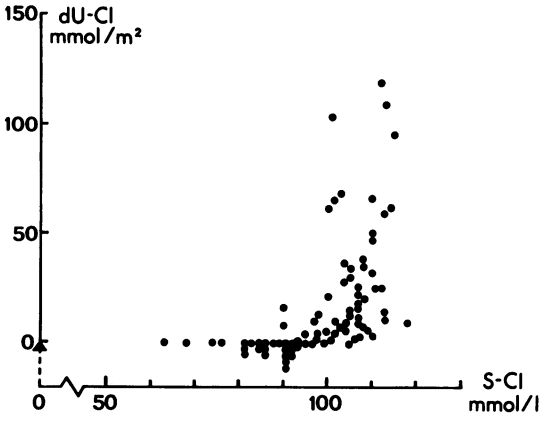

Fig. 6 *Relationship of serum Cl^- concentration to daily urinary (dU) Cl^- excretion in CCD patients.*

chloriduria depended on the serum Cl^- concentration. Only serum Cl^- levels below about 95 mmol/l were associated with absence of chloriduria, which is therefore characteristic of inadequately treated CCD only.

Electrolyte and acid-base status. The clinical picture of these untreated patients conformed with that described earlier for CCD: hypokalaemia and hypochloraemia with metabolic alkalosis. Their serum Na^+ concentration was normal (Table 2). This situation differs from that in the newborn in whom a hypochloraemia is associated with hyponatraemia (Fig. 5). In older patients the organism probably reacts to the hyponatraemia and dehydration (of which the serum Cl^- concentration is an indicator) with hyperaldosteronism (Holmberg, 1977). Na^+ absorption and K^+ excretion are stimulated both in the kidney and intestine (Fordtran and Ingelfinger, 1968; Sharp and Leaf, 1973) resulting in normonatraemia and hypokalaemia. Because of the high net intestinal and renal H^+ excretion, HCO_3^- accumulates and a metabolic alkalosis results.

Growth and development. Before treatment, weight and longitudinal growth of CCD patients was retarded. The 4 patients who were diagnosed late (RKo, AS, LI, AT) showed at age 6 months a mean deviation of $-1{\cdot}9$ SD (range $-1{\cdot}1$ to $-3{\cdot}0$ SD) from the height expected for their age and parental height. Their weight was even more retarded. The children were in poor general condition, wasted, and inactive. MK, the oldest patient we treated, was in poor condition during the first 3 years of life because of inadequate replacement therapy and at the age of 1 year had marked osteoporosis (Fig. 7). His serum Ca^{++} was $2{\cdot}9$ and inorganic P $1{\cdot}6$ mmol/l; urinary

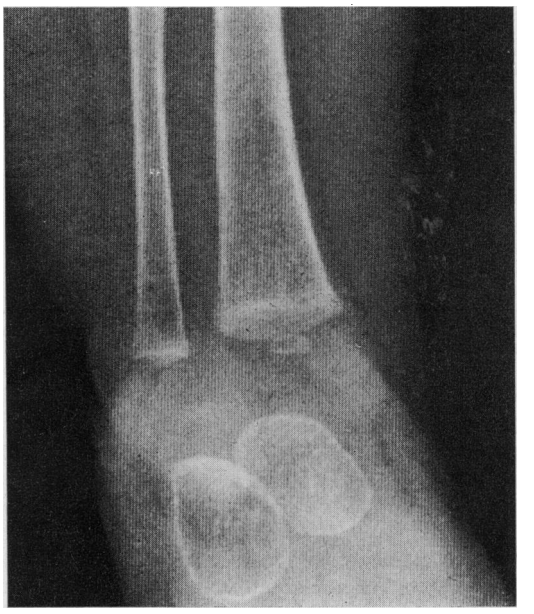

Fig. 7 *Ankle x-ray of patient MK at age 1 year showing marked osteoporosis.*

concentration of Ca^{++} was $1{\cdot}1$ and inorganic P $35{\cdot}1$ mmol/l; urine was Cl^--free. LI had a spontaneous fracture of the humerus at the age of 4 months and was unable to sit at 14 months. Untreated patients evidently have poor mineralization of bones owing perhaps to a loss of phosphate into the urine. AT developed surprisingly well, presumably due to her large spontaneous intake of salt and water. In our early patients delayed bone maturation (Greulich and Pyle, 1959) paralleled retarded growth.

Diagnosis. After the neonatal period hypokalaemia, hypochloraemia, and metabolic alkalosis are common but not inevitable. There is a history of prematurity and hydramnios. The final diagnostic criterion is the high faecal concentration of Cl^-. However, in severely and chronically dehydrated and hypoelectrolytaemic infants this concentration was as low as 40 mmol/l. It (again) always exceeded 90 mmol/l once the dehydration and hypochloraemia had been corrected.

Treatment

Table 5 shows how we treated all our patients. To our earlier patients we gave only KCl at a dose sufficient to maintain normal serum electrolyte levels. Most of them, however, remained slightly alkalotic and their urine was Cl^--free (Pasternack *et al.*, 1967). When examination of renal biopsy specimens

Table 5 *Chloride substitution requirements of the CCD patients during the previously used KCl substitution and the present NaCl+KCl substitution*

	Age		
Treatment	0–1 yr	3–6 yr	8–11 yr
KCl	100 (47–195) n=7	99 (60–204) n=10	68 (45–95) n=3
NaCl+KCl as KCl	124 (80–216) 48 (20–108) n=10	155 (60–171) 47 (12–85) n=7	89 (68–130) 34 (11–43) n=8

For criteria of adequate dose, see text. The mean (range) of dose is given, in mmol/m² per 24 h.

showed hypertensive arteriolar changes, juxtaglomerular hyperplasia, nephrocalcinosis, and hyalinized glomeruli in the presence of high renin, angiotensin II, and aldosterone activities (Pasternack and Perheentupa, 1966; Pasternack *et al.*, 1967), it was clear that our mode of replacement therapy was not satisfactory. Whereas high K^+ intake enabled Na^+ to be spared, it evidently did so through a hormonal adjustment that caused arteriolar pathology (Holmberg *et al.*, 1977). Therefore, since 1972 we have used a NaCl solution and added only enough KCl to meet the individual need for K^+.

Newborns. Replacement therapy must be started immediately. Once the existing extracellular deficits are corrected, the child needs approximately 10 mmol Cl^-/kg (1–2 mmol as KCl and the rest as NaCl) in iso-osmolal solution every 24 hours intravenously from the first day of life, in addition to normal requirements. These amounts are then adjusted for weight and serum electrolyte concentrations. If acidosis develops the dose is reduced. Peroral feeding can be started immediately in small amounts every 2–3 hours, the portions being gradually increased depending on weight and abdominal distension. Frequent insertion of a rectal tube helps to control distension. Peroral electrolyte replacement can usually be started on the third or fourth day, the dose being slowly increased and the intravenous dose correspondingly reduced. With our most recent patients we successfully moved to full oral feeding and electrolyte substitution by the age of 3 to 4 weeks. For oral replacement we used a 0·7% NaCl–0·3% KCl solution. To those patients in whom hyponatraemia and hyperkalaemia tended to develop on this solution a 0·9% NaCl–0·2% KCl solution was given for the first 4–5 months. The dose is adjusted to achieve normal serum electrolyte concentrations and *p*H and to maintain some chloriduria, conditions henceforth referred to as *adequate condition*. The infants were discharged when their weight exceeded 3 kg, which in recent years occurred by the time they were 2–3 months old.

Older patients. Patients received the 0·7% NaCl–0·3% KCl solution until about the age of 3 years. There after, for practical reasons, they were given a more concentrated solution together with free allowance of water. Because a slight hypokalaemia often tended to develop at this stage, the proportion of K^+ was increased. Hence the solution of older patients, taken in 3–4 daily doses at meals, contained 1·8% NaCl and 1·9% of KCl. The smallest dose was given which would maintain chloriduria. If hypokalaemia and alkalosis persisted on this dose, the concentration of KCl in the solution was increased to 2·2% to achieve normal *p*H and K^+ concentration. The required daily dose of Cl^- per m² of body surface area varied for each patient but decreased slightly with age (Table 5). The parents made the solution, 1 litre at a time, from preweighted portions of the salts, and boiled water.

Acute exacerbations. Electrolyte balance remained labile and was disturbed even by slight infections. Gastrointestinal infections with diarrhoea and vomiting, though not unusually frequent, were especially disruptive. When substitution was interrupted because of vomiting, and fluid loss was increased owing to an acceleration of the diarrhoea, a life-threatening degree of dehydration developed with unusual speed. This state was associated with hypoelectrolytaemia, and an extremely rapid loss of K^+. Volume had to be corrected *vigorously* to limit further loss of K^+, and up to 10 mmol K^+ per kg were needed during the first 24 hours. In such an acute state sufficient water and electrolytes must be given (1) to replace volume and concentration deficits, (2) to provide the normal substitution dose of the patients, and (3) to provide the requirements of a normal child of the same size. All water and electrolytes must be given intravenously and nothing should be given orally until rehydration is achieved, and vomiting has stopped.

Later course; with treatment

Diarrhoea. Fig. 8 shows stool composition at different ages. Osmolality was lower than in the ultrafiltrate of normal stools (Wrong *et al.*, 1965). Cl^- concentration was high, *p*H low, and HCO_3^- absent. The concentrations of the other ions were normal except for a low Mg^{++} concentration. Because volume was greater than normal, however, the daily excretion of this ion was in the normal range. For this same reason, excretion of Na^+ and K^+ were increased. Diarrhoea did not subside with

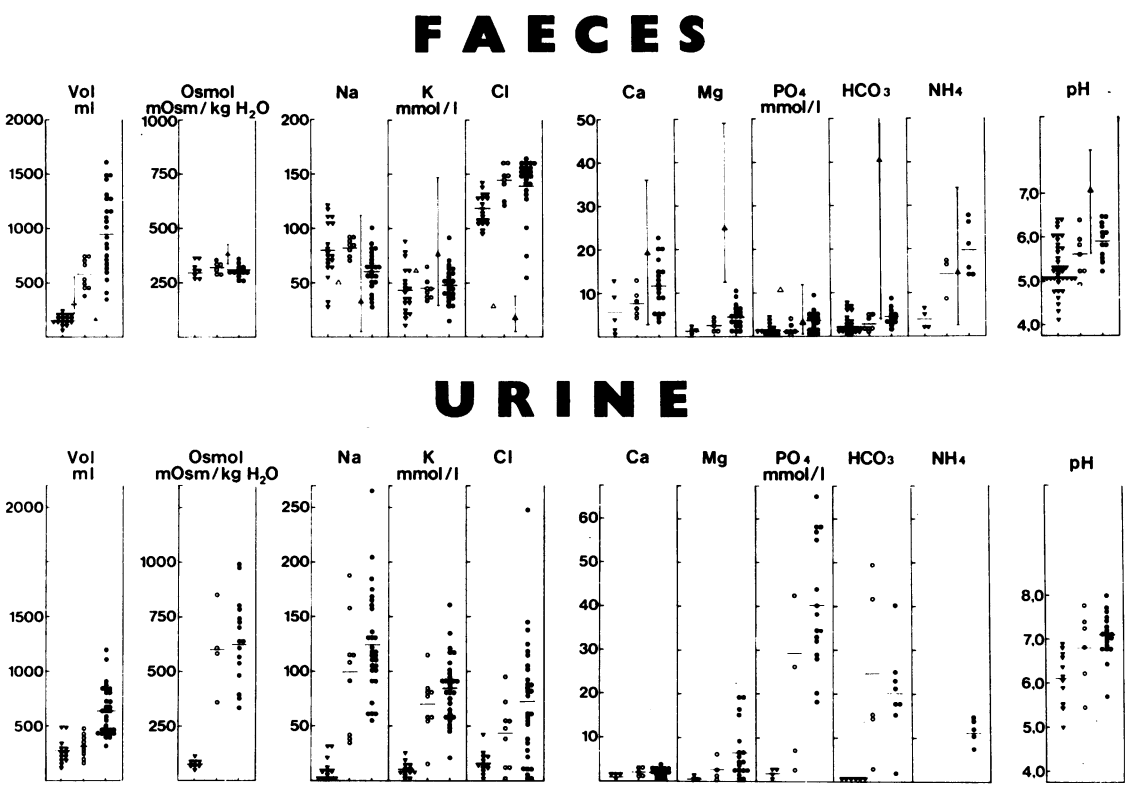

Fig. 8 *Electrolyte composition of faeces and urine in CCD patients at different ages* (▼ = *<3 m;* ○ = *1–3 yr;* ● = *6–12 yr*). *All patients were in adequate condition when the collecions were made.* △ = *normal mean (with range for volume) for diarrhoeal stools in infants* (*Holt* et al., *1915*) *and* ⏄ = *mean and range for concentrations of faecal dialysates from older normal subjects* (*Wrong* et al., *1965*). Conversion: SI to traditional units—Ca: 1 mmol/l ≈ *4·0 mg/100 ml. Mg: 1 mmol/l* ≈ *2·4 mg/100 ml.* PO_4: *1 mmol/l* ≈ *3·1 mg/100 ml.*

increasing age. On the contrary, the absolute volume tended to increase slightly. With age Na^+ concentration fell whereas K^+ remained constant, and concentration of Cl^- rose slightly.

Interestingly, the faeces became more alkaline with age. This was associated with an increase in the faecal content of non-Na^+-K^+ cations, mainly NH_4^+. Whether NH_3 was produced by the mucosa or by bacteria is not known, but it presumably facilitated the absorption of Na^+ by binding H^+, which was secreted in exchange for Na^+. CCD children learned to control defecation later than normal. However, the 10 children over 7 years of age were dry during the day and defecated 3–5 times daily. 4 of them were always clean at night and 4 of them most nights. 2 soiled their bed regularly; one of them (MH) had an unusually profuse diarrhoea and the other (MK) severe psychological difficulties apparently unrelated to the disease. An increase in stool volume always accompanied respiratory infections.

Urine. Fig. 8 shows the composition of urine in patients in adequate condition. All had persistent chloriduria. Na^+ and K^+ concentrations and the Na^+ –K^+ ratio were within normal limits indicating normal aldosterone activity. *p*H tended to be abnormally alkaline, a tendency that became more pronounced with age. This alkalinity was evidently due to the loss of H^+ into the intestine (Holmberg *et al.*, 1975), which left the balance of HCO_3^- to be excreted by the kidney.

Mg^{++} excretion was less than 0·06 mmol/kg. Ghazali and Barratt (1974) reported that in English children Mg^{++} excretion is normally $0{\cdot}116 \pm 0{\cdot}032$ (SD) mmol/kg. Hence Mg^{++} excretion in our patients was depressed. Excretion of all other ions was in the normal range. Glucosuria and aminoaciduria were not observed. Renal handling of Cl^-, Na^+, and K^+, and renal concentrating capacity appeared to be normal. Fig. 9 shows the relationship between the urinary Na^+–K^+ ratio and the serum Cl^- concen-

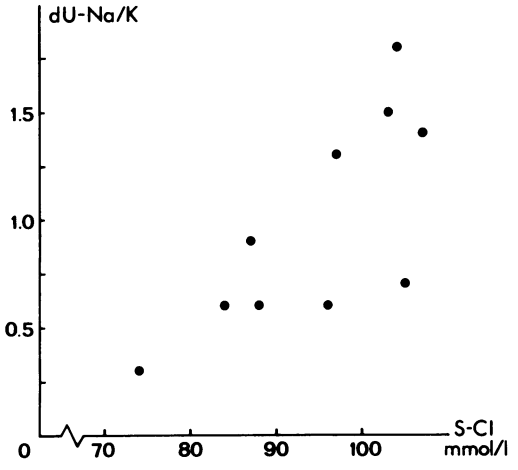

Fig. 9 *Relationship of (dU) urinary* $Na^+ - K^+$ *ratio to serum* Cl^- *concentration in patient SA.*

tration, which reflects extracellular volume (Holmberg, 1977). The kidney evidently reacted normally to increased aldosterone activity. Acute situations with severe hypokalaemia and alkalosis were often seen associated with 'paradoxic aciduria'. Renal pathology, glomerular function, and the low Mg^{++} excretion will be discussed elsewhere (Holmberg *et al.*, 1977; Holmberg, 1977).

Laboratory investigations. Ileal and rectal biopsies were performed; tests for antibodies against gluten and cows' milk protein were made; and faecal fat and sugars, serum Fe and total iron binding capacity, urinary amino acids, 17-ketogenic and 17-ketosteroids, growth hormone and cortisol responses to insulin hypoglycaemia were determined in those patients whose growth remained retarded during treatment (MH, LI, PI, and AS). All findings were normal. Repeated estimations showed serum Ca^{++}, inorganic phosphate, and alkaline phosphatase concentrations to be normal. Because high serum concentrations of uric acid have been reported in CCD (Gorden and Levitin, 1973; Pearson *et al.*, 1973) this was measured but was normal (n=19, mean±SD 3·4±1·1 mg/100 ml (0·2±0·07 mmol/l); normal range 2·5–5·5 mg/100 ml (0·15–0·32 mmol/l).

Growth and physical findings. In our early patients physical development was retarded in the first years of life but thereafter proceeded normally when treatment was adequate. The height of the oldest patient MK at age 3 years showed a deviation of −4·0 SD from the height expected for age and parental height but had caught up to −0·6 by his present age of 14·5 years. Our 4 youngest patients did not show any essential deviation from the expected height at the age of 6 months in contrast to the untreated patients (see above). The mean deviation from expected height at the latest observation was −0·2 SD (range −2·1 to +2·0) for all patients, and their weight was also normal.

Those children whose diarrhoea was profuse and whose electrolyte loss was therefore difficult to substitute for, had a distended abdomen. KR (Fig. 10a) was an extreme example. Most infants, however, did not have a prominent abdomen (Fig. 10b–d). Yet when examined radiographically the intestinal loops of the patients were distended with fluid and

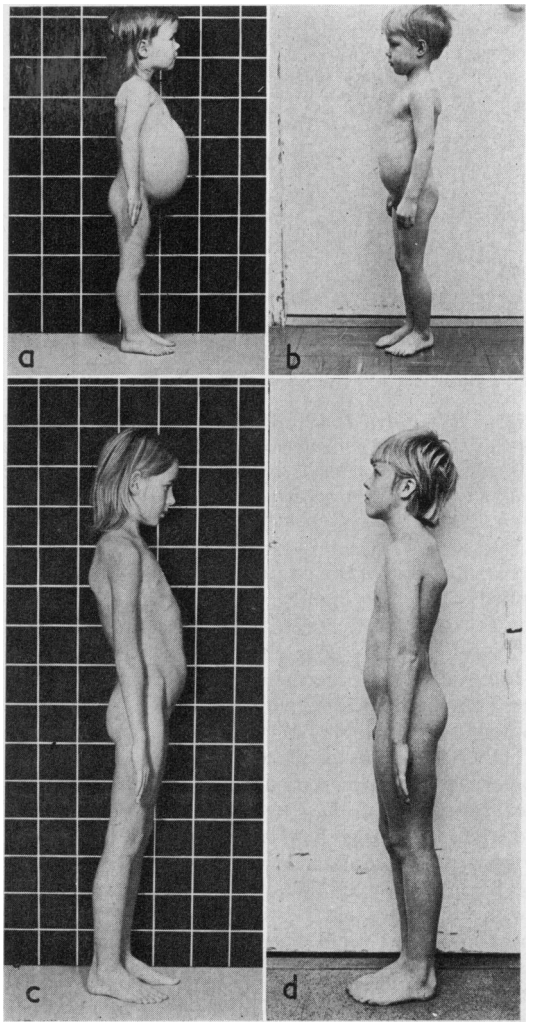

Fig. 10 *CCD patients KR, HP, RKo, and JH at ages 3, 4, 9, and 10 years (see text).*

air, which led the radiologist to diagnose an ileus if he did not know the child had CCD. Otherwise, the appearance of the children was normal and all had normal blood pressure. Enamel hypoplasia of the teeth was common in the early patients but not in the later ones. All patients had a reduced incidence of dental caries (Myllärniemi and Holmberg, 1975).

Intellectual and motor development. Mental retardation has been associated with CCD (Darrow, 1945; Kelsey, 1954; Duyck, 1955; Owen, 1964; Tucker, *et al.*, 1964; Harteman, 1966; Yssing and Friis-Hansen, 1966; Hager-Malecka *et al.*, 1973). Of our 18 living patients, 10 have reached school age. 8 attend a regular school and perform normally; 2 are in a special class for slow learners, performing the best in their group. Patient AT, in whom the diagnosis was made at 24 months, performed for her age and had developed normally except for retarded growth.

Nine of the schoolchildren were evaluated psychometrically; 2 performed at a good mean level for their age, 4 at a low normal level, and 3 subnormally. Testing of all preschool children failed to show any retardation. Our early patients had slightly retarded motor development in infancy but no neurological abnormality could be detected later. The more recent patients all had normal motor development. We do not have exact psychometric data on the sibs of our patients and hence cannot make a comparison of performance within families.

Severe neonatal jaundice and prolonged poor condition owing to insufficient substitution seem to have resulted in slight mental retardation in some of our early patients. Adequate treatment from birth almost certainly assures normal intellectual and psychomotor development.

Accompanying diseases. In the first years of life most patients had frequent respiratory infections. HP had pleurisy and empyema at the age of 1 year; the left basal lobe was resected and he has since done well. RJ had pneumonia with atelectasis of the lingula that was corrected with conservative therapy. TR had numerous bouts of pneumonia. A bronchial biopsy and bronchoscopic examination at the age of 3 showed slight changes of chronic bronchitis. At the age of 4 she still occasionally had pneumonia.

Urinary tract infections were frequent in our early patients but are rare with our present mode of treatment (Holmberg *et al.*, 1977). AS had occasional bloody stools; a rectal biopsy and sigmoidoscopic examination at the age of 12 showed a nonspecific colitis. Otherwise the children did well and after the first 2–3 years needed only yearly check-ups.

Discussion

That CCD is inherited as an autosomal recessive trait was shown by Norio *et al.* (1971) and has since been corroborated. Of 3 patients from outside Finland, one was the product of incest (Harteman, 1966), one of a marriage of first cousins (Yanagisawa *et al.*, 1968), and one of a marriage of halfsibs (McReynolds *et al.*, 1974). The families of the Finnish CCD patients have all come from the northern and eastern parts of the country, where the pool of other rare recessive genes is large (Norio *et al.*, 1973). Among our 18 families, 3 have each had 2 children with CCD and a total of 7 other infants have died, in retrospect probable cases of CCD. In the 21 families reported from outside Finland, 5 also had a probable case of CCD (Kelsey, 1954; Evanson and Stanbury, 1965, 2 cases; Davidson *et al.*, 1972; Pearson *et al.*, 1973). Sex distribution does not differ; of the 42 known patients, 23 were male and 19 female.

Perfusion studies have shown that lack or impairment of active Cl^-/HCO_3^- transport in the ileum and colon that result in faecal Cl^- loss and osmotic diarrhoea is probably the primary defect in CCD (Turnberg, 1971; Bieberdorf *et al.*, 1972; Pearson *et al.*, 1973; Holmberg *et al.*, 1975). Though faecal concentrations of Na^+ and K^+ are normal, there is a loss of these ions because stool volume is large. Perfusion studies have also shown that the impairment of Na^+ absorption is secondary to the acidity of the intestinal contents. Initial losses therefore are mostly of Cl^- and Na^+; accordingly, the first serum electrolyte disturbances we recorded were hypochloraemia and hyponatraemia. That those disturbances were detected already 1 hour after birth with hydramnios invariably present and meconium lacking is strong evidence of intrauterine diarrhoea. Evidence of prenatal disturbances was also noted in 17 of the non-Finnish patients: hydramnios in 9, prematurity or a birthweight below 2500 g in 8, and a lack of meconium in 2.

In the first days of life severe dehydration develops that is usually iso-osmolal, but may already then be markedly hypo-osmolal. In inadequately treated infants dehydration will always become hypo-osmolal during the first week. Serum K^+ concentration may remain normal and a distinct alkalosis at this stage is rare. If no treatment is instituted serum Na^+ content rises to normal concentrations and hypokalaemia, hypochloraemia, and metabolic alkalosis develop. The body compensates for the electrolyte disturbance through an increase in the absorption of Na^+ and water in the kidney and intestine at a cost of a loss of K^+ in these organs. The alkalosis probably develops partly through an associated increase in

H^+ excretion and partly through an absence of HCO_3^- secretion in the ileum and colon.

All our early patients, i.e. those not diagnosed at birth and in whom replacement therapy was inadequate, had renal involvement. They were slightly alkalotic, had hyperaldosteronism, and no chloriduria. Similar histories and clinical findings along with similar results in renal biopsy examinations have been reported for 4 non-Finnish patients; 2 were diagnosed at 6 months of age (Hager-Malecka *et al.*, 1973; McReynolds *et al.*, 1974), one at 2 years (Hartemann, 1966), and one at 6 years (Loeb *et al.*, 1970). Examination of renal biopsy specimens taken from our more recent patients in whom adequate substitution was made from birth showed that renal histology was normal and renal function unimpaired. Hence renal involvement is not a primary feature of CCD but develops as a result of inadequate replacement therapy (Holmberg *et al.*, 1977). Our findings speak against any specific renal tubular defect and the intestinal defect affects only Cl^-/HCO_3^- transport.

Several attempts at reducing the diarrhoea have been made. Evanson and Stanbury (1965) reported success with Cl^- restriction and $KHCO_3$ therapy, but we as well as others (Davidson *et al.*, 1972; Pearson *et al.*, 1973; McReynolds *et al.*, 1974) have failed. Our patients went into severe dehydration and hypoelectrolytaemia. Pearson *et al.* (1973) tried codeine phosphate, diphenoxylate hydrochloride, synthetic polysaccharide, and an anion exchange resin but failed to reduce the faecal volume. The only situation in which we have observed reduction of diarrhoea has been chronic hypovolaemia and hypoelectrolytaemia, which clearly is an undesirable state for the patient (Holmberg, 1977).

Retarded mental development has been attributed to CCD in 8 patients (see above). 2 were diagnosed at the age of 1 month, the others between the ages of 6 months and 2 years and hence all had experienced a long period of severe fluid disturbance in early life. Their early treatment cannot be evaluated from the reports. Of our patients, the early poorly treated ones has slight retardation of mental, statural and skeletal development. Our later patients in whom adequate replacement therapy was begun at birth manifest no such retardation. We thus feel justified in concluding that with adequate substitution CCD children develop normally.

The diagnosis of CCD is simple. It can be tentatively made from the typical history of hydramnios, prematurity, and watery diarrhoea, and then confirmed from the high faecal concentration of Cl^-. Serum electrolyte and *p*H changes are not reliable diagnostic criteria. Without treatment most children die in infancy but some will achieve a spontaneous electrolyte balance and survive with retarded psychomotor development. The extreme example is the patient of Pearson *et al.* (1973) in whom the diagnosis was made when he was 21 years old. Because the severity of the disease varies with each patient, the composition and amount of the electrolyte solution needed also varies. Optimum therapy should fully substitute for the faecal loss of Cl^-, Na^+, K^+, and water. The best criteria of adequate substitution are normal serum electrolyte concentrations, normal blood *p*H, and the presence of slight chloriduria. Thus, treatment in CCD aims at substituting for the diarrhoea, and in fact maintaining it. According to present knowledge, all attempts to stop or alleviate it are futile and dangerous. The patients will learn to live with their diarrhoea and to make an adequate social adjustment.

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Addendum

Since this paper was written we have seen one more patient with CCD, born in 1976 after 36 weeks' gestation as the second child of his family. The first child had been a stillbirth after a pregnancy complicated with hydramnios. There was again hydramnios. The infant's birthweight was 2540 g, and Apgar score 6. He was not doing well and did not gain weight: 'loose stools' were noted. At the age of 3 weeks serum Na^+ was 116, K^+ 3·0, and Cl^- 80 mmol/l. CCD was suspected and the child transferred to our hospital. The stool composition was Na^+ 76, K^+ 50, and Cl^- 112 mmol/l (after correction of deficits). The child has been doing well on the 0·7% NaCl–0·3% KCl solution, and was discharged at the age of 7 weeks with a weight of 3300 g.