Peptic perforation of the duplication had occurred at both ends. There was a small communication between the duplicated bowel and ileum. The lesion and adjacent bowel were excised without difficulty and the child recovered uneventfully.

Discussion

The use of ^{99m}Tc pertechnetate to aid in the diagnosis of Meckel's diverticula has become accepted practice (Rodgers and Youssef, 1975). Its usefulness in 2 cases of cystic duplications of the bowel has also been reported recently (Schwesinger *et al.*, 1975).

Tubular duplications of the bowel account for only 10% of enteric duplications (Daudet *et al.*, 1967). The condition may present with poorly localised recurrent abdominal pain, gastrointestinal bleeding, anaemia, gastrointestinal obstruction, or as an intrathoracic mass (Gross *et al.*, 1952). Tubular intestinal duplications are rarely palpable or visualised with barium contrast studies; hence preoperative diagnosis is infrequent (Sieber, 1956; Rios-Dalenz *et al.*, 1965). Heterotopic gastric mucosa may be present similar to that found in Meckel's diverticula. Daudet *et al.* (1967) reported 14 of 44 tubular duplications to have gastric epithelium. Gastric acid secretion and ulceration may result in pain and bleeding from the adjacent intestinal mucosa, in a manner strikingly similar to that associated with Meckel's diverticula.

^{99m}Tc pertechnetate is secreted by the surface gastric epithelial cells (Berquist *et al.*, 1975), is easily administered, has a short half-life (6 hours), and emits only gamma irradiation (Rodgers and Youssef, 1975). The scan is similar to that associated with Meckel's diverticula or cystic intestinal duplications in that the activity increases in step with increasing gastric activity. On the other hand, the scan obtained with tubular intestinal duplications differs from that obtained with Meckel's diverticula and cystic intestinal duplications in the diffuseness of the activity. There is a generalised increase in activity along the duplication rather than increased activity in an isolated area. 'False positive' scans include intussusception, Crohn's disease, meningomyelocele, ureteral obstruction, solitary kidney, bowel haemangioma, and aortic aneurysm (Rodgers and Youssef, 1975).

Summary

Preoperative identification of tubular duplication of the bowel is possible by the use of technetium 99m pertechnetate if gastric mucosa is present within the duplicated bowel. A case of a 4-year-old boy with abdominal pain is described. The scan showed

diffuse activity which increased in step with gastric activity.

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Acute neonatal and benign citrullinaemia in one sibship

Acute neonatal and benign citrullinaemia—

The spectrum of clinical presentation in citrullinaemia (argininosuccinic acid synthetase deficiency, Fig.) is wide, ranging from a rapidly fatal course in the neonatal period to normal or near normal development (Wick *et al.*, 1973). It has generally been assumed that ammonia occupies the key position in the pathogenetic process, the extent of the enzymatic impairment determining the frequency and severity of hyperammonaemic episodes and hence the prognosis. As in many inborn errors of metabolism the picture is complicated by genetic heterogeneity (Kennaway *et al.*, 1975). We report here on a family with 2 affected sibs, of whom one had the disease in the acute neonatal form while the development of the other has been essentially normal up to the age of 7 years.

Fig. The Krebs urea cycle (simplified).

Case reports

Case 1. A female infant born in hospital at term by normal delivery after an uneventful pregnancy, birthweight 3280 g and Apgar score of 7. She was discharged at 48 hours taking bottle feeds. On the sixth day grunting respiration, reluctance to feed, and a generalised rash prompted admission to hospital. On arrival she was unrousable, hypertonic, and opisthotonic, with normal fontanelle tension and absent reflexes, and had generalised skin mottling. The only other abnormal findings were grunting respirations and abdominal distension.

A presumptive diagnosis of septicaemia possibly with meningitis was made, and treatment started with dextrose-saline infusion, ampicillin, gentamicin, and diazepam. Examination of the CSF, blood count, serum electrolytes, and routine urine tests were normal.

During the following 24 hours the baby had periods of apnoea and cyanosis, developed urinary retention and hypotonia, and died 36 hours after admission. Necropsy 3 hours later showed diffuse pulmonary haemorrhage as the only noteworthy pathological finding. The brain was unfortunately not preserved for study. Reports received after death showed *Staphylococcus albus* in the blood cultures and a high level of citrulline in the urine.

Case 2. The first-born child of the same parents. When first seen at age 5½ years he had always been

well apart from infantile eczema and tonsillitis. Examination showed a small, thin boy: weight at the 3–10th centile, height at 3rd centile, and head circumference 50th centile. The hair was normal. At first, progress at a normal primary school was satisfactory, but at age 7 years he was considered immature and lacking in concentration. On formal psychological assessment his IQ was 94 on the Wechsler Intelligence scale for children (WISC, verbal scale 90, performance scale 100). Electroencephalogram showed a nonspecific generalised abnormality.

At age 7 years 4 months he presented with a 48-hour history of drowsiness, confusion, and ataxia. No signs of infection were found and within a short time of receiving 5% dextrose by infusion, he had fully recovered. His mother thought he had had two milder but similar episodes, one of which had followed tonsillitis.

His urine contained a large quantity of orotic acid and his serum glutamine level was high (Table). An electroencephalogram was regarded as normal. Future management will be a low protein diet, monitoring of the urinary orotic acid, and possibly arginine supplements.

Methods

Amino acids were assayed by ion-exchange chromatography using a Locarte amino acid analyser and sodium acetate buffers including the precautions

Table Biochemical findings in a family with citrullinaemia

	Plasma (mmol/l)		Urine (mol/mol creatinine)		Skin fibroblasts ASA synthetase ($\mu\text{mol/h per g protein}$)
	Citrulline	Glutamine	Citrulline	Orotic acid	
Controls	0.01–0.05	0.52–0.69	0–0.1	$1.5\text{--}5.0 \times 10^{-3}$ $\dagger 0.5\text{--}3.5 \times 10^{-3}$	76, 116
Father	0.045	—	—	—	53
Mother	0.085	—	—	—	46
Case 1	—	—	11.3	3.9×10^{-3}	—
Case 2	—	—	—	—	12
Age 5 yr	2.3	0.62	3.5	7.4×10^{-3}	—
Age 7 yr in hospital	2.0	1.16	5.7	90×10^{-3}	—

*Age 0–4 weeks; †age 6 months–10 years. ASA = argininosuccinic acid.

Conversion: SI to traditional units—Citrulline: 1 mmol/l $\approx$ 17.5 mg/100 ml. Glutamine: 1 mmol/l $\approx$ 14.6 mg/100 ml.

outlined by Palmer *et al.* (1974). Orotic acid was estimated by a modification of the method of Rogers and Porter (1968). Standard cultures of skin fibroblasts were grown in a medium consisting of 77.5% TC medium 199, 20% newborn calf serum, and 2.5% chicken embryo extract. Cell harvesting for enzyme assays was carried out after the third passage of all cell lines. Argininosuccinate synthetase was assayed by a radiochemical procedure using the substrate mixture for liver (Levin, 1971) to which had been added ureido ^{14}C citrulline, 0.2 $\mu\text{Ci/ml}$. The urea formed was separated by paper chromatography and its radioactivity measured.

Results

The single specimen of urine collected from Case 1 by catheterisation during a period of oliguria, showed after chromatography a large excess of citrulline with high levels also of glutamine. Otherwise the amino acid pattern showed no significant abnormalities. The urine glutamine level was 7.3 mol per mol creatinine; the normal ratio for infants of 2 days to 3 months is 0.1 to 0.5. Urine urea was 58 mmol/l (0.35 g/100 ml). No positive identification could be made of any pyrimidine metabolites. Apart from an intense citrulline peak, the urine amino acid pattern for Case 2 was normal. When seen at the age of 5 years his plasma citrulline level was 100 times normal, other amino acids were within the normal range and the excretion of orotic acid was only slightly raised (Table). Blood urea was 5.0 mmol/l (30 mg/100 ml); urine urea 450 mmol/l (2.7 g/100 ml). In contrast, during a hyperammonaemic episode at the age of 7, both the plasma glutamine and orotic acid excretion were greatly increased despite little alteration in his citrulline level (Table). N-acetyl citrulline was detected in the urine of both cases.

Discussion

The urine amino acid pattern for Case 1 was typical of citrullinaemia. The greatly increased urinary excretion of glutamine probably reflects detoxication of ammonia. On the other hand, the normal level of orotic acid suggests that in this case there was no excess of carbamyl phosphate and therefore most likely no uncompensated hyperammonaemia. Roerdink *et al.* (1973) described a rapidly fatal case with high plasma citrulline and high urinary glutamine but normal blood ammonia. Ammonia intoxication thus appears to be a sufficient but not a necessary factor in the precipitation of neonatal crises in citrullinaemia. Though high levels of plasma citrulline may be toxic particularly in the neonate, the history of Case 2 confirms that they may also be compatible with

normal intellectual development. Hyperammonaemic crises triggered by infections or other stress are still liable to occur in citrullinaemia (Thoene *et al.*, 1977) as in other disorders of the Krebs urea cycle.

The comparatively high enzyme activity found in the fibroblasts of Case 2 might indicate a variant form of citrullinaemia, and Case 1 was presumably affected by the same mutation. Studies of the kinetics of the affected enzyme, of levels of other enzymes of the urea cycle, and of unaffected reference enzymes will be necessary to establish this point. In most recorded cases enzyme levels have ranged from non-detectable to 3 or 4% of control values (Roerdink *et al.*, 1973; Kennaway *et al.*, 1975; Thoene *et al.*, 1977), up to 20% in two Swiss patients (Wick *et al.*, 1973). A level of 30% normal has been reported in an older child less severely affected (Matsuda *et al.*, 1976).

Case 2 had a normal plasma arginine level of 0.075 mmol/l (1.3 mg/100 ml). Normal levels have been reported in other less severely affected cases (Case 3, Wick *et al.*, 1973; Matsuda *et al.*, 1976) in contrast to those found in the fatal neonatal form (Case 2, Wick *et al.*, 1973; Roerdink *et al.*, 1973; Thoene *et al.*, 1977). Obviously the lower the enzyme activity, the greater the dependence upon exogenous arginine and the less the chance of survival. Even comparatively high enzyme levels may not afford adequate protection, particularly in the neonatal period if adverse environmental factors supervene. A wide spectrum of clinical manifestations even within the same sibship should not be altogether unexpected.

Summary

Citrullinaemia was diagnosed in an infant who died at age 8 days. The clinical picture was of the disease in its acute neonatal form. A sib has a blood citrulline of 100 times normal and about 10% of normal argininosuccinic acid synthetase activity in cultured fibroblasts. Clinically he is normal with an IQ of 94 on the Wechsler Intelligence Scale for Children.

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Sources of error in estimation of glomerular filtration rate from plasma creatinine concentration in children

Sir,

Counahan *et al.* (1976) introduced a new simple method of estimating glomerular filtration rate (GFR) by means of plasma creatinine concentration (P_c) and body height (Ht) using formula $GFR (ml/min \text{ per } 1.73 \text{ m}^2) = 0.43 \text{ Ht (cm)}/P_c \text{ (mg/100 ml)}$. Recently Szelid and Méhes (1977) showed in a large group of children without renal disease that the conventional 24-hour creatinine clearance correlates well with the GFR estimated by the Ht/ P_c method. However the usefulness of the latter method demands that P_c be stable and that creatinine production be within normal limits, so that P_c reflects only the excretory function of the kidneys.

Congenital nephrotic syndrome of Finnish type (CNF) is characterised by massive proteinuria, poor somatic growth, and slow deterioration of renal function (Hallman *et al.*, 1973; Huttunen, 1977). On account of the decreased muscular mass in proportion to body weight, creatinine production and consequently P_c of patients with CNF is low.

We have compared the GFR estimated by the Ht/ P_c method with the 24-hour endogenous creatinine clearance (24-hour C_c) in 61 measurements of 15 CNF children under the age of 2 years, and in 67 children and young adults with acquired renal disease aged from 9 months to 20 years. Plasma and urinary creatinine were determined as true creatinine after absorption of noncreatinine chromogens by Lloyd's reagent (Henry *et al.*, 1974). The results are shown in the Fig. The correlation between the two methods is satisfactory in both groups, but in CNF children the mean of the 24-hour C_c is $17.3 \text{ ml/min per } 1.73 \text{ m}^2$ lower than that of the GFR estimated by the Ht/ P_c method; while in the children with acquired renal disease the 24-hour C_c is $8.2 \text{ ml/min per } 1.73 \text{ m}^2$ higher than the result from the Ht/ P_c method on average. The

mean of P_c in CNF children was 0.41 mg/100 ml ($36.2 \text{ } \mu\text{mol/l}$) with a range of $0.16\text{--}1.84 \text{ mg/100 ml}$ ($14.1\text{--}162.7 \text{ } \mu\text{mol/l}$), and that of the children with acquired renal disease 0.69 mg/100 ml ($61 \text{ } \mu\text{mol/l}$) with a range of $0.26\text{--}7.40 \text{ mg/100 ml}$ ($23\text{--}654 \text{ } \mu\text{mol/l}$). The 24-hour urinary excretion of creatinine per kg body weight of CNF children was $8.6 \pm 2.5 \text{ mg}$ and that of the children with acquired renal disease $16.5 \pm 4.1 \text{ mg}$; the difference between the two groups is significant at the level of $P < 0.001$.

Creatinine is to some extent excreted by the renal tubular cells (Arant *et al.*, 1972). Thus somewhat higher values are expected from the conventional 24-hour C_c than from the Ht/ P_c method in children with normal creatinine production. On the other hand, in CNF children with low creatinine production the Ht/ P_c method obviously overestimates the true GFR, and in this peculiar situation the conventional creatinine clearance is more accurate than the Ht/ P_c method in the estimation of GFR. No doubt the Ht/ P_c method is reliable and generally suitable to clinical work, but it must be remembered that it gives false results when P_c is not in equilibrium or when the endogenous creatinine production is low.

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