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## Treatment of Inborn Errors of Urea Synthesis — Activation of Alternative Pathways of Waste Nitrogen Synthesis and Excretion

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## TREATMENT OF INBORN ERRORS OF UREA SYNTHESIS

### Activation of Alternative Pathways of Waste Nitrogen Synthesis and Excretion

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**Abstract** Children with inborn errors of urea synthesis accumulate ammonium and other nitrogenous precursors of urea, leading to episodic coma and a high mortality rate. We used alternative pathways for the excretion of waste nitrogen as substitutes for the defective ureagenic pathways in 26 infants. These pathways involve synthesis and excretion of hippurate after sodium benzoate administration, and of citrulline and argininosuccinate after arginine supplementation.

The children were treated for seven to 62 months;

**UNTREATED** inborn errors of urea synthesis are fatal when the clinical presentation is that of neonatal hyperammonemic coma.<sup>1</sup> Therapy with peritoneal dialysis, essential amino acids, or their nitrogen-free analogues has increased survival.<sup>2</sup> However, all but one of these infants died before one year of age.<sup>3</sup> The physiologic defect in these patients is an inability to synthesize and excrete waste nitrogen in the form of urea. This defect allows nitrogenous precursors of urea, glutamine, alanine, and ammonium to accumulate.

We designed a study to test the hypothesis that other endogenous pathways for the synthesis and excretion

of waste nitrogen might substitute for the abnormal ureagenic pathway<sup>4</sup> (Fig. 1). The choice of the pathway to be used depended on the enzymatic defect. In deficiencies of argininosuccinate synthetase (EC 6.3.4.5) and argininosuccinase (EC 4.3.2.1), the accumulated substrates that appear in the urine — citrulline and argininosuccinate — may serve as waste nitrogen products because they contain the nitrogen normally destined for urea synthesis. Their synthesis and excretion is enhanced by arginine supplementation. The administration of sodium benzoate further diverts ammonium nitrogen from the defective urea pathway to hippurate synthesis by way of the glycine cleavage complex.

We studied the effects of benzoate administration in patients with deficiencies of carbamyl phosphate synthetase (EC 2.7.2.2), ornithine transcarbamylase (EC 2.1.3.3), and argininosuccinate synthetase. We report below the long-term results of such alternative-pathway therapy in 23 neonates presenting in hyperammonemic coma caused by an inborn error of urea synthesis and in three children whose siblings had died in neonatal hyperammonemic coma and who were themselves found to have a urea-cycle enzymatic de-

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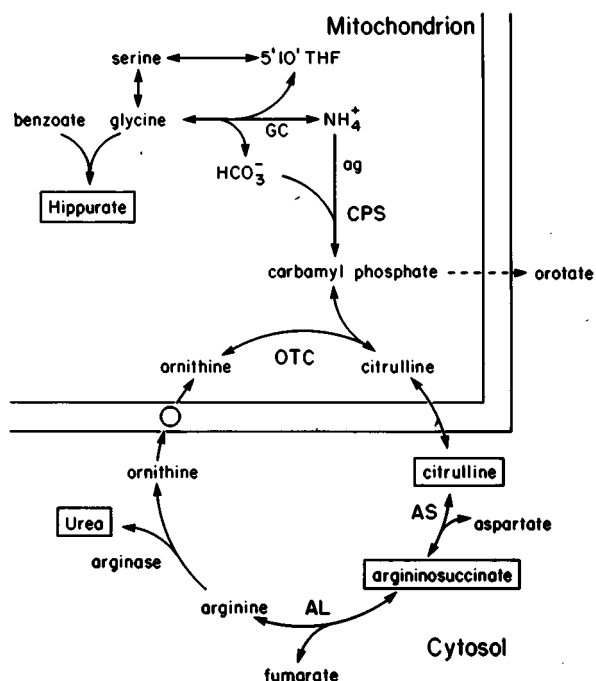


Figure 1. Pathways of Waste Nitrogen Synthesis and Excretion. The abbreviation ag denotes acetyl glutamate (a cofactor for carbamyl phosphate synthetase (CPS); AL, argininosuccinase; AS, argininosuccinate synthetase; OTC, ornithine transcarbamylase; 5'10' THF, 5'10' methylene tetrahydrofolate; and GC, glycine cleavage complex. The excretion products are shown in the boxes. The open circle in the mitochondrial membrane denotes an ornithine transporter.

fect in the newborn period. Twenty-two of 26 infants are alive at ages ranging from seven to 62 months (mean  $\pm$  S.D.,  $20 \pm 15$ ).

## PATIENTS

Twenty-six patients were studied (Table 1). Twenty-three were identified because they were in neonatal hyperammonemic coma. Ten of these infants had siblings who had died in coma in the newborn period; three of these 10 were treated prospectively from birth.

The specific enzymatic defect was suggested by the plasma citrulline and argininosuccinate levels and by urinary orotate excretion.<sup>4</sup> Diagnosis through determination of enzymatic activity in appropriate tissue (liver, skin fibroblasts, or erythrocytes) was made in 21 patients. Mean activity was  $2.0 \pm 4.9$  per cent of normal ( $\pm$  S.D.) (Table 1). Coma lasted from two to 30 days (median duration, three days). Plasma ammonium levels ranged from 351 to 2000  $\mu$ mol per liter (mean  $\pm$  S.E.M.,  $1002 \pm 96$ ).

## Management of Hyperammonemic Coma

Intravenous infusion of sodium benzoate, 0.25 g per kilogram of body weight, was followed by constant infusion of 0.25 to 0.5 g per kilogram per day. A dose of arginine hydrochloride, 0.8 g per kilogram, was followed by a constant infusion of 0.2 to 0.8 g per kilogram per day. Peritoneal dialysis was also required during neonatal hyperammonemic coma in 20 of 23 patients. Episodes of post-neonatal hyperammonemia were treated with intravenous benzoate or arginine or both.

## Long-Term Therapy

We designed long-term therapy according to the specific enzymatic defect. In infants with argininosuccinase deficiency, a protein-restricted diet (1.5 to 2.0 g per kilogram per day) was supplemented

with arginine as the free base (0.5 to 0.7 g per kilogram per day in three or four divided doses).

Infants with argininosuccinate synthetase deficiency received sodium benzoate (0.25 g per kilogram per day), arginine (0.5 to 0.7 g per kilogram per day), a diet low in milk protein (0.5 to 0.7 g per kilogram per day), and essential amino acids (0.5 to 0.7 g per kilogram per day).<sup>5</sup> Supplemental calories were provided as Formula #80056 (Mead Johnson, Evansville, Ind.) in order to maintain intake at no less than 100 kcal per kilogram per day. In children more than nine months of age, this formula was supplemented with low-protein solids in an exchange diet.

Infants with carbamyl phosphate synthetase and ornithine transcarbamylase deficiencies were given sodium benzoate (0.25 g per kilogram per day), arginine (0.2 g per kilogram per day), essential amino acids (0.5 to 0.7 g per kilogram per day) and milk protein (0.5 to 0.7 g per kilogram per day). The total nitrogen intake was equivalent to that found in a protein intake of 1.7 g per kilogram per day.

## METHODS

In nine patients studied at the Johns Hopkins Hospital the plasma ammonium levels were measured by a cation-exchange method, which has a normal range of 15 to 30  $\mu$ mol per liter.<sup>6</sup> Amino acids were measured in plasma by automated ion-exchange chromatography. Total urinary nitrogen and its components were measured as previously described.<sup>7</sup> Benzoate and hippurate were determined by reverse-phase high-pressure liquid chromatography as follows. Plasma and urine samples were diluted to 1:4 with 100 per cent methanol containing *p*-aminobenzoate as an internal standard. Aliquots of the supernatants or standard solutions were injected into a Waters C<sub>18</sub> column. The mobile phase consisted of 5 mM phosphoric acid in 10.5 per cent methanol used at a flow rate of 1.5 ml per minute. The effluent was monitored at 232 nm. In the patients with argininosuccinase deficiency, urinary argininosuccinate and its anhydrides were estimated as equivalents of  $\alpha$ -amino nitrogen.<sup>8</sup> (In such patients; whose urine contains large amounts of argininosuccinate, urinary amino acids other than argininosuccinate are excreted in normal amounts and thus contribute little to the  $\alpha$ -amino nitrogen content.<sup>9</sup>) In argininosuccinate synthetase deficiency  $\alpha$ -N-acetylcitrulline and citrulline appear in the urine<sup>10</sup>; in this study they were isolated together by anion-exchange chromatography and measured as total ureido chromogen, according to the method of Prescott and Jones.<sup>11</sup> Expression of urinary citrulline nitrogen excretion therefore included both citrulline and  $\alpha$ -N-acetylcitrulline nitrogen.

Because children with complete defects in the urea cycle have little or no capacity to synthesize urea, we used the concept of "effective" urinary waste nitrogen. "Effective" waste nitrogen excludes all urinary urea nitrogen, half the argininosuccinate nitrogen, and two thirds of the citrulline nitrogen; the source of two of the nitrogen atoms of these molecules is assumed to be dietary arginine.

The IQ of infants under five months was determined by developmental assessment. In children six months to 2½ years old the Bayley Scale of Infant Development was used. Thereafter the Stanford-Binet Intelligence Scale was employed. The significance of differences was measured by Student's *t*-test.

The study was performed between 1978 and 1982 and involved a collaborative effort between 26 medical institutions in the United States and Europe. It was approved by the institutional review board of each participating hospital, and informed parental consent was obtained. Oral and intravenous sodium benzoate are Investigational New Drugs approved for human use by the Food and Drug Administration.

## RESULTS

### Prospective Treatment

Six neonates were known to be at risk for one of the diseases because a sibling had died in the newborn period of hyperammonemic coma caused by an inborn error of urea synthesis. In each of these six, the therapeutic measures described above were started when the infants were 50 hours old but before the diagnosis

Table 1. Clinical and Laboratory Features of 26 Infants with Defective Urea Synthesis.

DEFICIENT ENZYME/PATIENT NO.	AGE/SEX	DURATION OF NEONATAL COMA	PEAK NEONATAL PLASMA AMMONIUM	POST-NEONATAL HYPERAMMONEMIA	FAMILY HISTORY	ENZYME ACTIVITY †	IQ	OUTCOME ‡
	mo	days	$\mu\text{mol/liter}$	no. of episodes		% of normal		
<b>Carbamyl phosphate synthetase</b>								
1*	18/M	3	1300	4	—	20§	80	A
2*	14/M	0	60	4	+	ND¶	100	A
<b>Ornithine transcarbamylase</b>								
3	18/M	3	400	1	+	0	100	D
4*	22/M	3	450	0	+	0	100	A
5	11/M	30	715	3	+	0	36	D
6	8/M	0	50	6	+	0	100	D
7*	10/M	5	2000	1	+	0	30	A
8	8/M	4	1500	0	+	ND	100	A
9	8/M	5	1140	0	—	0	50	A
<b>Argininosuccinate synthetase</b>								
10	42/F	4	887	7	+	0**	65	D
11	34/M	4	1153	5	—	1	52	A
12	27/F	3	1500	2	+	0**	38	A
13	19/F	5	1800	4	+	0**	63	A
14	19/F	4	1000	1	—	0**	57	A
15	10/F	3	700	1	—	ND	100	A
16	8/F	5	500	0	—	0**	40	A
<b>Argininosuccinase</b>								
17	62/F	4	530	3	—	0††	80	A
18	50/F	4	854	10	—	0††	54	A
19	34/M	3	1280	4	—	0	50	A
20	31/F	0	40	3	+	3**	78	A
21	26/M	4	1300	3	—	0††	50	A
22	23/M	1	351	1	—	ND	56	A
23	16/F	3	600	1	—	ND	60	A
24	16/F	1	700	0	+	0††	100	A
25	9/M	3	1600	0	—	0††	100	A
26	7/M	2	780	0	+	0††	100	A

\*Because these patients had increasing intolerance to protein, phenylacetate (0.25 g per kilogram per day) was added to provide another pathway of waste nitrogen synthesis and excretion via phenylacetylglutamine,<sup>7</sup> which accounted for 40 per cent of "effective" waste nitrogen excretion. Preliminary results in Patients 3, 10, and 18 have been reported elsewhere.<sup>3</sup>

†ND denotes not determined.

§The total activity of carbamyl phosphate synthetase in the liver was 55 per cent of normal; however, because the coupling enzyme used in the assay was contaminated with activity of this enzyme, the corrected value is suspect.

¶The activity of carbamyl phosphate synthetase in the liver of this patient's affected brother was 2 per cent of normal.

||Determined in liver.

\*\*Determined in skin fibroblasts.

††Determined in erythrocytes.

was established. After 24 to 48 hours, three of the neonates with suspected ornithine transcarbamylase deficiency were found to have plasma citrulline levels above 7  $\mu\text{mol}$  per liter — a finding not compatible with a complete deficiency of carbamyl phosphate synthetase or ornithine transcarbamylase. A normal diet was then instituted, and development progressed normally. There has been no evidence of toxicity from the early therapy.

The three other children were also treated from birth: one had elevated plasma levels of citrulline and argininosuccinate, and the other two had no detectable citrulline in plasma at 24 to 48 hours of age. On the basis of these data and the diagnoses of the previously affected siblings, these patients were diagnosed as having deficiencies of argininosuccinase, carbamyl phosphate synthetase, and ornithine transcarbamylase. None of these children had symptoms during the newborn period, but all subsequently had episodes of hyperammonemia, one of which resulted in death.

#### Post-Neonatal Episodes of Hyperammonemia

Sixty-four post-neonatal episodes of hyperammonemia occurred in 19 of the 26 patients (Table 1).

The precipitating causes included excessive protein intake, interruption of medications, and intercurrent infections. Mean plasma ammonium levels ( $\pm$ S.E.M.) were  $251 \pm 17$   $\mu\text{mol}$  per liter on admission and fell to  $86 \pm 8$  within six hours of intravenous arginine and benzoate therapy during 61 episodes. In three other episodes plasma ammonium ( $420 \pm 68$   $\mu\text{mol}$  per liter on admission) did not fall significantly; neither subsequent peritoneal dialysis (in Patient 10) nor hemodialysis (in Patients 3 and 6) was successful in preventing a fatal outcome. In the surviving children no deterioration in neurodevelopmental status was evident after the hyperammonemic episodes.

#### Growth and Neurologic Sequelae

The neurologic and developmental outcomes varied from normal intellectual and motor function to severe mental retardation and cerebral palsy (Table 1). There appeared to be a relation between the magnitude of hyperammonemia, the duration of coma, and the progress in neurologic development. Less severe hyperammonemia and brief coma or absence of coma were associated with improved neurological outcome. Among the 23 survivors of neonatal hyperammonemic

coma, 10 had normal development, seven had mild mental retardation (IQ of 52 to 68), and six had moderate to severe mental retardation (IQ below 52). One of the severely retarded children (Patient 5) was found dead in bed one morning although he had been well the previous night. The intellectual function of the three infants who were treated prospectively was within the normal range.

The most recent length, weight, and head circumference of each child is plotted in Figure 2. Length was normal in 20 children and below the fifth percentile in six; weight was normal in 19. Head circumference was in the normal range in 20 children and below the fifth percentile in six.

### Biochemical Studies

Nine patients were studied at Johns Hopkins Hospital. Their mean plasma ammonium level ( $\pm$ S.E.M.)

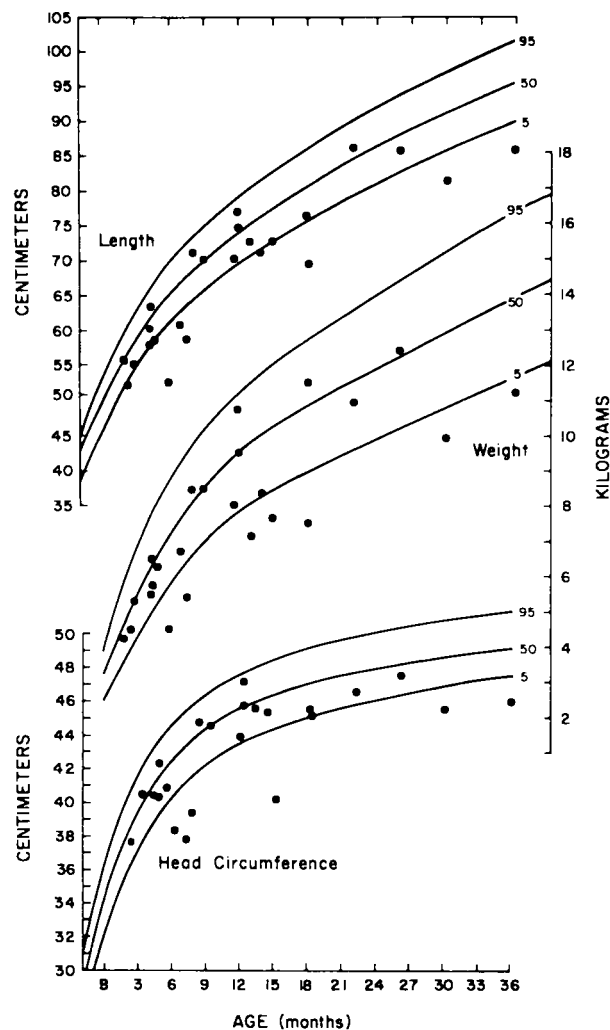


Figure 2. Recent Measurements of the Length, Weight, and Head Circumference of the Study Patients, Plotted on a Normal-Population Growth Curve.<sup>12</sup>

The two oldest patients are not represented: at 42 and 48 months, respectively, their heights were in the fifth percentile and their weights and head circumferences were in the 25th percentile.

was  $35.5 \pm 1.9 \mu\text{mol}$  per liter. In the patients with ornithine transcarbamylase and carbamyl phosphate synthetase deficiencies, who received arginine (0.2 g per kilogram per day — about 1 mmol per kilogram of body weight), fasting plasma arginine levels were  $60.9 \pm 10.4 \mu\text{mol}$  per liter. In the patients with argininosuccinate synthetase and argininosuccinase deficiencies, who received 0.5 to 0.7 g of arginine per kilogram per day, plasma arginine levels were slightly elevated —  $127.6 \pm 19.4 \mu\text{mol}$  per liter. Plasma citrulline levels were  $3936 \pm 958 \mu\text{mol}$  per liter in the patients with argininosuccinate synthetase deficiency, and plasma argininosuccinate levels were  $907 \pm 599 \mu\text{mol}$  per liter in the patients with argininosuccinase deficiency. The mean plasma glycine level remained normal ( $190.6 \pm 11.9 \mu\text{mol}$  per liter) in patients receiving benzoate. Plasma levels of other amino acids were within normal limits. Plasma levels of benzoate and hippurate were  $1.2 \pm 0.3$  and  $2.2 \pm 0.6$  mg per deciliter, respectively.

Table 2 shows the percentage of “effective” waste nitrogen contributed by alternative pathways in these patients. In the patients with ornithine transcarbamylase and carbamyl phosphate synthetase deficiencies, hippurate nitrogen accounted for 28 to 48 per cent of the total “effective” urinary waste nitrogen excretion. In those with argininosuccinate synthetase deficiency, 33 to 37 per cent of “effective” waste nitrogen was derived from citrulline nitrogen and hippurate nitrogen. In those with argininosuccinase deficiency, 52 to 59 per cent of “effective” waste nitrogen was derived from argininosuccinate nitrogen.

### Side Effects and Toxicity

Arginine, benzoate, and essential amino acids were well tolerated, although intravenous benzoate (0.25 g per kilogram) given over 30 minutes occasionally caused vomiting. Intravenous arginine hydrochloride (0.8 g [4 mmol] per kilogram) occasionally caused acidosis.

The following laboratory studies of hematopoietic, renal, and hepatic function were performed bimonthly in the patients: determination of electrolytes, glucose, creatinine, total protein, albumin, thyroxine, prothrombin time, cholesterol, bilirubin, triglycerides, and serum aspartate and alanine aminotransferases, urinalysis, and complete blood count. All results were within normal limits except for levels of serum aspartate aminotransferase, which were slightly elevated in all patients ( $77 \pm 16$  IU per liter). Levels of serum alanine aminotransferase were normal or near normal. Pathological examination of the liver in three patients revealed normal hepatic tissue except for a small amount of fibrosis — findings similar to those of LaBrecque et al.<sup>13</sup> There was no evidence of fatty infiltration or inflammation. Hepatomegaly was found only in patients with argininosuccinase deficiency, in whom the liver was palpable 5 to 9 cm below the costal margin.

Two episodes of benzoate intoxication occurred.

The effects of one of these episodes is shown in Figure 3. This child (Patient 18) inadvertently received an oral dose of 0.8 g of benzoate per kilogram over 24 hours. She vomited and became irritable. The plasma benzoate level, which had been less than 5 mg per deciliter, increased to 123 mg per deciliter, and urinary hippurate excretion increased from 78 to 290 mmol per 24 hours. Urinary excretion of argininosuccinate did not change from 31 mmol per milligram of creatinine. Plasma glycine fell from 345 to 64  $\mu$ mol per liter, and ammonium decreased from 40 to 16  $\mu$ mol per liter. Sodium benzoate was discontinued, the symptoms disappeared, and the abnormal values returned to the levels before intoxication within 24 hours. The child with the other episode of intoxication had a similar course.

### DISCUSSION

All but one of the previously described patients with urea-cycle enzymatic defects who presented in neonatal hyperammonemic coma died by one year of age.<sup>1</sup> Urea-cycle enzymatic activity was less than 10 per cent of normal in these patients, in contrast to children presenting with symptoms later in childhood, who have greater than 10 per cent normal activity.

Our therapeutic approach to inborn errors of urea synthesis relies on the use of alternative pathways of waste nitrogen synthesis and excretion (Fig. 1), with protein restriction and, except in cases of argininosuccinase deficiency, dietary supplementation of essential amino acids. The usefulness of these approaches is suggested by studies of the partition of urinary nitrogen, which show that 28 to 59 per cent of total "effec-

Table 2. Percentages of Total "Effective" Waste Nitrogen Contributed by Alternative Pathways in Nine Patients.

MISSING ENZYME/ PATIENT NO.	AGE	EXCRETION BY ALTERNATIVE PATHWAY *			
		HIPPURATE NITROGEN	CITRULLINE NITROGEN	ARGININO- SUCCINATE NITROGEN	TOTAL
		<i>per cent of effective waste nitrogen</i>			
<i>Carbamyl phosphate synthetase</i>					
1	4	37	—	—	37
2	3	48	—	—	48
<i>Ornithine trans-carbamylase</i>					
4	7	28	—	—	28
7	3	31	—	—	31
<i>Argininosuccinate synthetase</i>					
11	4	21	12	—	33
13	12	23	12	—	35
10	15	11	26	—	37
<i>Argininosuccinase</i>					
19	12	—	—	59	59
20	43	—	—	52	52

\*Effective waste nitrogen includes one third of citrulline nitrogen and one half of argininosuccinate nitrogen.

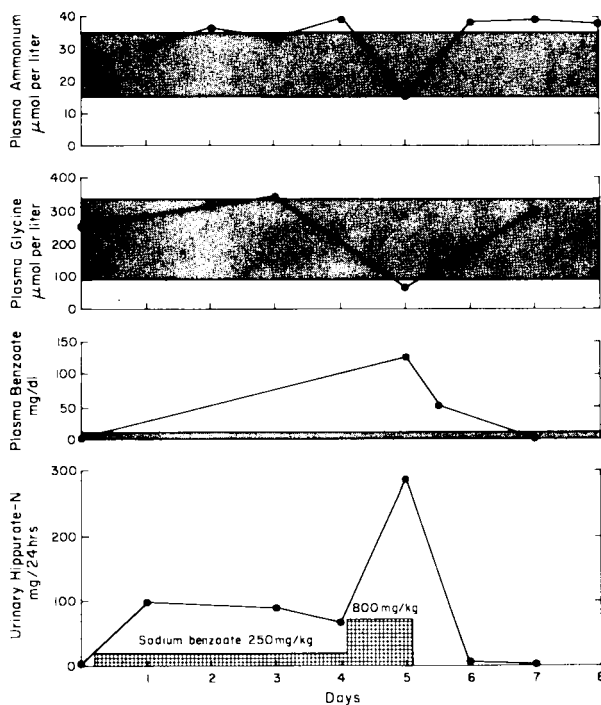


Figure 3. Effects of Sodium Benzoate Intoxication in a Patient with Argininosuccinase Deficiency (Patient 18).

The shaded areas indicate normal ranges for plasma benzoate, glycine, and ammonium, and the hatched area indicates the daily dose of sodium benzoate. When the dose was increased from 250 to 800 mg per kilogram, plasma benzoate and urinary hippurate excretion increased, and plasma glycine and ammonium levels decreased.

“effective” urinary nitrogen is contributed by alternative pathways of nitrogen synthesis and excretion.

No serious side effects have been observed in our experience with over 18 patient-years of sodium benzoate therapy. Although acute benzoate toxicity induced vomiting and lethargy, these symptoms resolved within 12 hours of discontinuation of the drug and only occurred when plasma benzoate exceeded 80 mg per deciliter.

Neurologic and developmental progress has been variable. Half the children have had delayed intellectual development. This delay was evident from infancy and appears to be the result of neonatal hyperammonemic coma. Development since infancy has not regressed but has been comparable to that observed in infants with brain damage resulting from perinatal asphyxia.<sup>14</sup> These data suggest that persistently high levels of plasma citrulline or argininosuccinate may not be toxic.

Intercurrent episodes of hyperammonemia appeared to result from excessive protein intake, infections, or withdrawal of medications. These episodes were managed with intravenous benzoate plus arginine. However, in three of 64 episodes, hyperammonemia responded neither to these measures nor to hemodialysis or peritoneal dialysis, and the children died.

Although the eventual outcome in these patients remains to be determined, the use of alternative pathways of waste nitrogen synthesis and excretion combined with dietary nitrogen restriction appears to control hyperammonemia, prolong life, and improve outcome.

*Note added in proof:* After submission of this manuscript, Patient 7 died during an episode of untreated hyperammonemic coma.

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## SPECIAL ARTICLE

### COST EFFECTIVENESS OF LEAD SCREENING

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**Abstract** Lead-screening programs may reduce childhood disabilities, but at what cost? Through a review of the literature, we performed a cost-effectiveness analysis in which the costs, savings, and health benefits of two lead-screening strategies — employing either a free erythrocyte protoporphyrin assay or blood lead measurement — were compared with each other and with a strategy of no screening in a population of three-year-old children.

When the prevalence of lead poisoning among the children screened is 7 per cent or more, we estimate that free

erythrocyte protoporphyrin screening averts morbidity and results in net savings: It is both better and cheaper than no screening.

At prevalences below 7 per cent, the net positive costs from screening and early treatment must be weighed against the noneconomic benefits of improved quality of life and considered in relation to other investments that could be made to benefit society. At all prevalence rates, free erythrocyte protoporphyrin screening is more cost effective than blood lead screening. (*N Engl J Med*. 1982; 306:1392-8.)

**L**EAD is poison. When lead is ingested by children, usually as lead-based paint, it can accumulate in their bodies to levels high enough to cause encephalopathy, abdominal pain, or anemia. At lower levels, it may cause subtler disturbances in learning, impulse control, and dexterity. As information about the toxicity of low-level lead burdens has accumulated, the diagnostic thresholds for lead poisoning have fallen steadily.

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ily.<sup>1-5</sup> Risks remain particularly high among black, Hispanic, and poor children.

In 1978, the Center for Disease Control published guidelines<sup>6</sup> developed by its Ad Hoc Advisory Committee on Childhood Lead-Based Paint Poisoning Prevention. These guidelines considered alternative methods and schedules for screening, defined four different risk classes that were based on the results of screening tests, and proposed standards for the treatment and follow-up of children with positive screening tests. These recommendations today provide the framework for the conduct of many local and state screening programs, which test hundreds of thousands of children each year.

The Center for Disease Control report recommended the use of the free erythrocyte protoporphyrin