the anti-metabolite per kilo of diet all died. When the dosage of PGA was increased to 100 mg/kg the rats at the 3.0 mg/kg level survived, but no protection was noted at the 10 mg/kg level of anti-metabolite. In the chick, the same investigators[10] found a slight inhibition of growth by 3 mg of the antagonist per kilo of purified diet in the presence of 0.1 mg/kg of PGA. When the level of PGA was raised to 10 mg/kg, this inhibition of growth was prevented. Hertz and Tullner[11] found that with this compound inhibition of the estrogen induced response of the chick oviduct could be obtained by 3 daily subcutaneous injections of 0.2 mg each. Blocking of this inhibition was demonstrated with 3 daily doses of 5 mg each of PGA given subcutaneously one hour prior to the injection of the anti-metabolite.

With a closely related antagonist, 4-amino-PGA, the prevention by PGA of toxicity,[12,13] of inhibition of estrogen induced growth of uterus or oviduct,[11] and of the inhibitory effect against mouse leukemia[2] and solid tumors[4] has been observed.

It has been shown above that prevention of the toxic effects of these 2 analogs of PGA may be obtained within narrow ranges at the minimum toxic dose by high dosage of PGA. Since the dose of 4-amino-N^{10}-methyl-PGA used in these experiments was just below the toxic dose, it was to be expected that an effect obtained at this level might be counteracted by PGA. The ratio of PGA to anti-metabolite necessary to prevent this anti-leukemic effect was approximately similar to that required in other studies.[10,11] The ability of PGA and PTGA to prevent the anti-leukemic effects of this anti-metabolite would seem to lend support to the theory that the chemotherapeutic effect of this derivative is due to its action as a metabolic antagonist of PGA.

Summary. The effect of 4-amino-N^{10}-methyl-pteroylglutamic acid in prolonging the survival time of mice with transplanted leukemia Ak 4 can be blocked almost completely by prior administration of 10 to 20 times as much pteroylglutamic acid and, to a lesser degree, by 17 to 125 times as much pteroyltriglutamic acid.

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[11] Hertz, R., and Tullner, W. W., *Endocrinology*, 1949, **44**, 278.

[12] Franklin, A. L., Stokstad, E. L. R., and Jukes, T. H., PROC. SOC. EXP. BIOL. AND MED., 1948, **67**, 398.

[13] Philips, F. S., and Thiersch, J. B., *J. Pharm. and Exp. Therap.*, 1949, **95**, 303.

17256. Effect of Aluminum Hydroxide Gel and Calcium Lactate on Serum Bicarbonate.*

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The observations herein reported indicate that subjects with reduced kidney function respond to the oral administration of suitable amounts of calcium lactate and aluminum hydroxide gel with a marked and sustained elevation of serum bicarbonate. This response occurred both in very young infants with physiologically immature kidneys[1] and in older infants and children with kidney disease. No such increase in serum bicarbonate accompanied the administration of comparable amounts of the two agents to older infants and children with normal kidney function.

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[1] Barnett, H. L., Hare, K., McNamara, H., and Hare, R., *J. Clin. Invest.*, 1948, **27**, 691.

TABLE I.
Effect of Aluminum Hydroxide Gel and Calcium Lactate on Serum Bicarbonate.

Subject	Age, days	Wt., kg	Daily oral intake: 5% aluminum hydroxide gel, ml/kg	Daily oral intake: Ca-lactate g/kg	Serum bicarbonate content,[6] mM/L: Before treatment	During treatment,* days: 1	2	3	4	5
				Young infants.						
CA	1	4.2	10	1.6	27.0	26.8	33.5			
OR	2	3.2	7.5	1.5	24.7	26.2	32.3	34.1		
AD	2	3.6	11	1.3	20.9	25.0	29.1		27.3	26.7
FR	7	4.2	7	1.1	19.6		25.8	24.3	29.1	
JO	9	3.3	11	1.7	22.7	25.2	29.1	30.8		
RA	21	2.7	15	1.6	26.3	31.4	30.9	33.8		
NE	28	3.0	7	1.4	25.8	31.9	36.7			
				Children with kidney disease.						
	Years									
MA	1	7.5	10.0	1.5	16.2	20.2	24.0		25.7	26.0
		7.3	10.3	1.0	19.6	25.4	26.7		29.1	32.3
		7.5	10.0	1.0	19.5		24.3	25.5		
GR	14	33.0	3.9	0.6	21.5	25.4	28.3			26.2
				Infants and children with normal kidney function.						
AN	16 mos.	10.2	8.5	1.3	25.7	25.9	25.4	26.5		
UR	23 mos.	6.2	9.0	1.4	25.3	27.3	27.3	25.2		
BO	5½ yrs.	16.0	8.8	1.2	26.8	30.6	27.2	29.2		
AR	8½ yrs.	16.0	9.4	1.3	30.6	30.4		31.5		

* The last value coincides with the final day of treatment with both drugs. Serum bicarbonate values returned to pre-treatment levels within 24 to 48 hours following discontinuation of either or both drugs.

[6] Van Slyke, D. D., and Neill, J. M., *J. Biol. Chem.*, 1924, **61**, 523.

The quantities of calcium lactate and aluminum hydroxide gel given and the magnitude and rate of change in serum bicarbonate are shown in Table I.

Given separately, neither agent produced an increase in serum bicarbonate in subjects with either normal or reduced kidney function. Failure of aluminum hydroxide gel to raise serum bicarbonate in subjects with normal kidney function is in accord with earlier reports.[2] Its effect in subjects with reduced kidney function is less well established. Freeman and Freeman[3] gave this drug to children with chronic nephritis but did not report detailed data on serum bicarbonate. They did mention relief from acidosis a few days after adding aluminum hydroxide gel to the low phosphorus diet of a 10 year old boy with chronic renal insufficiency.[4] From our findings, correction of renal acidosis with aluminum hydroxide gel alone would not be expected. The apparent discrepancy may, perhaps, be explained by differences in phosphorus intake since our subjects received milk, and therefore relatively large amounts of phosphorus.

The mechanisms underlying the difference in response of serum bicarbonate in subjects with reduced and normal kidney function to calcium lactate and aluminum hydroxide gel are not yet explained. Detailed balance studies are now in progress in an attempt to define these mechanisms.

The observed increase in serum bicarbonate in subjects with reduced kidney function following oral calcium lactate and aluminum hydroxide gel is of interest in several respects. It is known that aluminum hydroxide gel alone lowers serum phosphate and raises serum calcium in patients with chronic renal acidosis.[3] Our results indicate that calcium lactate given with the aluminum hydroxide gel may correct the acidosis. The possible application of the combined use of the two drugs in the treatment of tetany of the newborn is under investigation. Finally, the fact that elevation of serum bicarbonate occurred in very young infants suggests that the ability of the immature kidney of young infants to excrete excess base may be less well developed than its ability to conserve base.[5] Observations are planned to study this function in young infants directly.

Conclusions. The combined oral administration of calcium lactate and aluminum hydroxide gel produced a marked and sustained elevation of serum bicarbonate in young infants with physiologically low kidney function and in older subjects with impaired function. This effect did not occur in subjects with normal kidney function. Given separately, neither drug produced an increase in serum bicarbonate in subjects with normal or reduced kidney function.

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[2] Kirsner, J. B., *Am. J. Digest. Dis.*, 1941, **8**, 160.

[3] Freeman, S., and Freeman, W. M. C., *Am. J. Dis. Child.*, 1941, **61**, 981.

[4] Freeman, S., and Freeman, W. M. C., *Quart. Bull. Northwestern U. Med. School*, 1943-45, **17-19**, 275.

[5] Gordon, H. H., McNamara, H., and Benjamin, H. R., *Pediatrics*, 1948, **2**, 291.

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