

SEATO Clinical Research Study on Bladder Stone*

Coordinator: Aree Valyasevi, M.D. Chief, Thai Component Clinical Research Center

Principal Investigators: Aree Valyasevi, M.D.
Sakorn Dhanamitta, M.D.**
Robert Van Reen, Ph.D.***

Assistant Investigators: Pichai Thuvasethakul, B.Sc. (in Pharm)
Jaratbhan Yooktatat, B.Sc. (in Pharm)
Potjane Threeratana, B.Sc. (in Pharm)
Thara Viriyapanich, B.Sc. (in Pharm)

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GENERAL INFORMATION

The results of a series of investigations from this Laboratory comprising 8 papers, were recently submitted for publication in the American Journal of Clinical Nutrition⁽¹⁻⁸⁾. The studies suggested that vesical calculus formation is a neo-natal disease and that the nutritional status of the mother fetus somehow contribute to the development of uroliths. The most pertinent findings can be summarized as follows:

1. Infant feeding practices differ markedly between families living in villages (hyper-endemic area) and in Ubol City (hypo-endemic area). Essentially all newborn in both locations are breast-fed. About 60% of village mothers started their infants on supplemental glutinous rice feedings during the first week of life, usually after the 3rd day. In the city, on the other hand, only 8% of the mothers stated they fed infants supplemental foods during the first 4 weeks of life and only 52% of the infants received rice during their first 3 months. If caloric requirements for infants are calculated on the basis of 115 ± 15 calories/Kg body weight/day, the glutinous rice fed village infants could supply about one-half their total daily requirement.

2. It was a fairly general observation that village women during pregnancy and lactation did not increase their intake of proteins or of foods in general. Deviations from their usual diets were only in the direction of greater food restrictions, particularly during the third trimester. This was done in the belief that it would result in a smaller infant and an easier delivery.

3. Twenty-four hour urine volumes were frequently less in village than in city newborn infants under 1 year of age, and in children 2 to 10 years old. This was not always observed but varied with season and location. The urinary osmolarity was generally lower in the village samples than in those from the city, and the total number of osmoles excreted in 24 hours was significantly lower in the village newborn less than 15 days old.

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** Medical Staff, Ubol Provincial Hospital, Dept. of Medical Services, Ministry of Health, Bangkok, Thailand

*** Chief, Nutrition Biochemistry Laboratory, Naval Medical Center, Bethesda, Md., USA

4. Significantly lower urinary phosphate concentrations and 24 hour excretion values were found in village samples of all age groups up to 1 year old compared with the city values. On the contrary, the urinary calcium concentration and 24 hour excretion value were somewhat higher in the village than in the city samples in the newborn age group. No differences could be demonstrated in the older age groups.

5. The 24 hour excretion of magnesium and of uric acid were very similar in both locations in all age groups up to 10 years of age. Oxalate excretion was also very similar in the subjects studied.

6. The total inorganic sulfate and the free inorganic sulfate in the urine were lower in village samples from boys up to 1 year of age than in city samples. This was true whether the data were expressed on the basis of concentration, 24-hour excretion, or related to creatinine excretion.

7. Oxalate crystalluria was observed in 12 of 28 village boys under 45 days of age. On the contrary, none of the 39 city infants of the same age group had oxalate crystalluria. Uric acid crystalluria was found equally in both village and city samples.

PUBLICATIONS

1. Halstead, S.B., and Valyasevi, A.: Studies of Bladder Stone Disease in Thailand. I. Introduction and description of studied area. *American Journal of Clinical Nutrition*.
2. Chutikorn, C., Valyasevi, A., and Halstead, S.B.: Studies of Bladder Stone Disease in Thailand. II. Hospital experience, urolithiasis at Ubol Provincial Hospital, 1956-1962. *American Journal of Clinical Nutrition*.
3. Halstead, S.B., and Valyasevi, A.: Studies of Bladder Stone Disease in Thailand. III. Epidemiology of Bladder Stone in Ubol Province. *American Journal of Clinical Nutrition*.
4. Valyasevi, A., Halstead, S.B., Pantuwatana, S., and Tankayul, C.: Studies of Bladder Stone Disease in Thailand. IV. Dietary Habits, Nutritional Intakes and Infant Feeding Practices Among Residents of Hypo- and Hyper-endemic Areas. *American Journal of Clinical Nutrition*.
5. Halstead, S.B., Valyasevi, A., and Umpaivit, P.: Studies of Bladder Stone Disease in Thailand. V. Dietary Habits and Disease Prevalence. *American Journal of Clinical Nutrition*.
6. Valyasevi, A., Halstead, S.B., and Dhanamitta, S.: Studies of Bladder Stone Disease in Thailand. VI. Urinary studies in children 2 to 10 years old, of hypo- and hyper-endemic area. *American Journal of Clinical Nutrition*.
7. Valyasevi, A., and Dhanamitta, S.: Studies of Bladder Stone Disease in Thailand. VII. Urinary studies in newborn and infants of hypo- and hyper-endemic areas. *American Journal of Clinical Nutrition*.
8. Van Reen, R., Valyasevi, A., and Dhanamitta, S.: Studies of Bladder Stone Disease in Thailand. VIII. Sulfate excretion by newborn and infants in three localities: the possible relationship of protein nutrition to vesical lithiasis. *American Journal of Clinical Nutrition*.

The occurrences of oxalate and uric acid crystalluria during the course of study are shown in Tables I and II. Four of 21 subjects of the phosphate trial did not show any oxalcrystalluria at any time during the study. One subject who was on an artificial milk formula, showed no cystalluria during the course of 30 microscopic examinations. The data in Tables I and II are presented in terms of the number of occurrences of crystalluria and the number of examinations made. It can be seen that when the infants received placebo, methionine or vitamin B₆, 23 to 29 percent of urine examinations revealed oxalcrystalluria, whereas none of the samples from infants receiving orthophosphate demonstrated oxalate crystals. Disappearance of the oxalcrystalluria usually occurred within 24 hours after the supplementation of phosphate.

The data suggest that milk supplementation is not as effective as orthoyhosphate in reducing the occurrence of oxalcrystalluria. However, it should be pointed out that all subjects rejected part of the milk in the first few days, some developed loose stools and the period of study war only six days. Therefore, it is possible that the amount of phosphate absorbed might be less from milk than from the orthophosphate supplementation.

A total of 60 urine examinations were also carried out on 4 infants whor were supplemented with milk feedings for 18 consecutive days. A total of 5 occurrences of oxalcrystalluria were observed. Three occurrences were found in one infant who had mild recurrent diarrhea and two occurrences were during the first two days of supplementation in another infant.

The data presented in Table I on oxalcrystalluria are totals of observed occurrences of crystalluria without regard to the sequence of supplementation. It is possible that when inorganic orthophosphate was administered there might be a carry-over into the next period of supplementation. To check this, the data were recalculated to determine the number of occurrences of oxalcrystalluria in infants receiving the placebo either before or after the orthophosphate supplementation. In the control group prior to phosphate administration, there were 14 occurrences out of 33 examinations or 42 percent. In the control group after the phosphate supplementation, there were 6 occurrences of oxalcrystalluria out of 35 examinations or 17 percent. It thus appears that there is a carry-over of the phosphate effect into the next supplementation period. No such carry-over effect was obvious in the cases of infants receiving milk after phosphate or placebo after milk. However, the number of cases in the present series is too small to draw any firm conclusions concerning carry-over effects and an experiment will be designed to test this.

The mean urine pH rose from 5.9 during the control period to 7.1 during the orthophosphate supplementation. To test whether there is a relationship between the alkalinity of urine and disappearance of the oxalcrystalluria, at the end of the regular study period, five infants were administered sodium bicarbonate (2 to 3 gm/day) for 6 days. A rapid rise in the urinary pH values was obtained but 9 out of 30 urine examinations still demonstrated oxalate crystals. The findings do not support the concept that alkalinity of the urine alone is involved in the disappearance of oxalcrystalluria.

Uric acid crystalluria (Table II) also appears to be reduced by supplementation with either orthophosphate or fat-free powdered milk, although uric acid crystals were not completely eliminated by phosphate, as in the case of oxalcrystalluria. It is possible that alkalinity of the urine was a factor in reducing the uric acid crystalluria during phosphate supplementation. However, no change in urinary pH was observed during the milk supplementation, therefore, further study will be required before any conclusion can be drawn. There was no obvious effect of methionine or vitamin B₆ supplementation on uric acid crystalluria.

From the data presented above it appears that the oral administration of inorganic orthophoshate will eliminate the oxalcrystalluria and probably reduce the uric acid crystalluria commonly found in village urine samples. Oral administration of DL-methionine and vitamin B₆ have no such effects. It must be determined in further studies whether the effect is a specific response to phosphate or whether other supplements will act in a similar manner.

The question immediately arises as to the mechanism(s) by which phosphate exerts its effect. It is known that dietary inorganic phosphate will reduce the absorption of calcium from the gastro-intestinal tract. In the present study, phosphate supplementation had a rapid effect on oxalocrystalluria, thus suggesting some other mechanism of action. Vermeulen et al⁽¹⁾ and Miller et al⁽²⁾ have indicated that many normal urinary components, such as citrate, urea, K, Na, SO₄, PO₄, Cl and Mg ions are all effective in increasing the solubility of calcium phosphate and calcium oxalate in water. It is expected that the phosphate and milk supplementations of the present study resulted in increased urinary excretion of phosphate.

Fleisch and Bisaz⁽³⁾ have indicated that pyrophosphate will inhibit both hydroxyapatite and calcium oxalate precipitation. Furthermore, Fleisch and Bisaz⁽⁴⁾ have demonstrated that the oral administration of orthophosphate to healthy subjects induces a significant increase in urinary pyrophosphate excretion. The determination of the concentrations of the various urinary components and ions mentioned above is now underway.

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3. Fleisch, H. and Bisaz, S.: The inhibitory effect of pyrophosphate on calcium oxalate precipitation and its relation to urolithiasis. Experimentia 20:279, 1964.
4. Fleisch, H. and Bisaz, S.: Effect of orthophosphate on urinary pyrophosphate excretion and the prevention of urolithiasis. Lancet. May 16, 1964, p. 1065.

Table 1

Occurrence of oxalcrystalluria in village infants following supplementation with a variety of substances

Supplement	No. of Infants	Oxalcrystalluria		
		No. of occurrences	No. of examinations	No. of infants with crystalluria
Placebo	17*	25	93	17
Orthophosphate	17	0	83	0
Milk	17	7	87	5
Placebo	14**	20	70	7
Methionine	14	20	70	10
Vitamin B ₆	14	16	70	11

* There were 17 of the original 21 infants who showed oxalcrystalluria at some time during the study.

** There were 14 of the original 19 infants who showed oxalcrystalluria at some time during the study.

Table II

Occurrence of uric acid crystalluria in village infants following supplementation with a variety of substances

Supplement	No. of Infants	Uric acid crystalluria		
		No. of occurrences	No. of examinations	No. of infants with crystalluria
Placebo	15*	22	83	15
Orthophosphate	15	6	73	3
Milk	15	10	77	5
Placebo	16**	11	80	7
Methionine	16	18	80	11
Vitamin B ₆	16	12	80	8

* There were 15 of the original 21 infants who showed uric acid crystalluria at sometime during the study.

** There were 16 of the original 19 infants who showed uric acid crystalluria at some time during the study.