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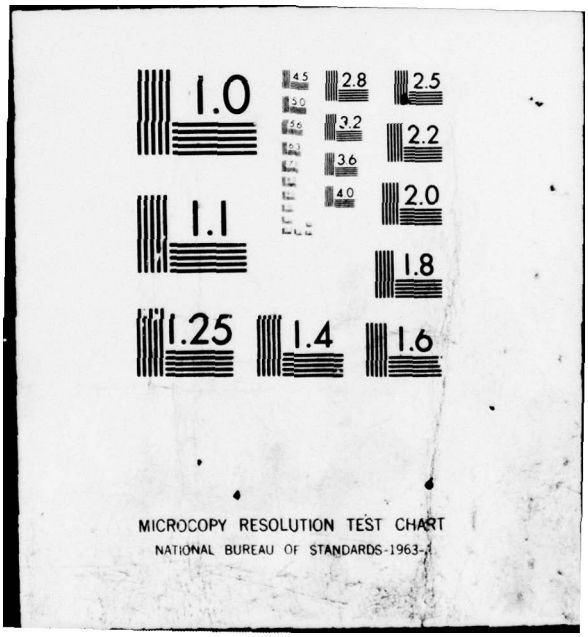
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Task No. NR 202-025

FINAL REPORT

# Kidney Stone Prevention

by

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24 May 1979

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number)
Idiopathic urinary bladder stone disease was studied in children living in Thailand, Pakistan, and Egypt. In Thailand the approach taken was to study subjects living in endemic and non-endemic stone areas to determine nutritional and biochemical differences between the two populations. In Egypt and Pakistan, patients with bladder stone disease were compared to subjects of the same age without stones.

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In the three countries, phosphate deficiency appeared to be the one common factor in stone patients or those living in endemic areas.

Oxalcrystalluria was frequently observed in Thai children living in endemic stone areas. In Egypt and Pakistan, oxalcrystalluria was almost always observed in children with stone disease. The oxalcrystalluria could be reduced or eliminated by daily supplements of inorganic orthophosphate.

It is thought that the availability of phosphate from foods may be a critical factor in the etiology of the disease. Many plant foods contain much of their phosphate in the form of phytates which are relatively unavailable.

Final Report under Contract N00014-67-0387-0011 and N00014-75-C-0357

Kidney Stone Prevention

(a) Summary of all research accomplishment:

The research conducted under this contract was divided into two components, namely: Project I. Clinical Investigation, and Project II. Laboratory Investigations. These two projects will be summarized separately.

Project I. Clinical Investigations

During the early period of the contract, investigations on stone disease were initiated in Cairo, Egypt; Karachi, Pakistan; and collaborative arrangements made to participate in stone studies in Bangkok, Thailand. The studies in Egypt were under the supervision of Dr. Adel Loutfi, Professor of Pediatric Surgery, Children's Hospital, Kasr el Aini, Cairo University, Cairo, Egypt who was also supported by ONR with PL 480 funds on Project NR 202-060. The studies in Pakistan were under the supervision of Dr. M. Ataur Rahman, Professor of Biochemistry, Jinnah Postgraduate Medical Center, Karachi, Pakistan who was also supported by ONR with PL 480 funds on Project NR 202-026. The studies in Thailand were supervised by Dr. Aree Valyasevi, Dean of the Medical Faculty, Ramathibodi Hospital, Bangkok, Thailand who also received support under a grant from the U.S. National Institutes of Health. Support was provided these groups in the form of supplies which could not be obtained locally, technical information concerning methods of analysis and experimental procedures to be followed, and by conducting a number of analytical procedures on samples sent to the University of Hawaii by the foreign collaborators.

The primary focus of the research was on idiopathic urinary bladder stone disease in children which occurs with considerable frequency in Egypt, Pakistan and Thailand. This approach was taken since it was felt that there was a greater possibility of finding the etiological factors involved than in the case of adult kidney stone disease, for the following reasons:

- idiopathic bladder stone disease in children in some countries is limited to specific geographic areas.
- the stones occur in very young children (as young as 6 months) thus the period of inititaion must be relatively short.
- the children in the rural areas of developing countries where stones are common eat relatively simple diets, thus a dietary etiology would be easier to uncover.
- the occurrence of stones in children is high in some localities (for example, about 4% of boys in rural N.E. Thailand would be expected to have a stone or presumptive symptoms of stones by age 10 years.
- the children in the rural areas do not move much, thus would be available for study.

The investigation took two approaches. In Thailand children in the rural areas of the N.E. developed bladder stones whereas those in the urban areas did not, thus it was possible to compare the two populations of children for the occurrence of stones, the presumptive symptoms of stones, nutritional differences and biochemical differences in blood and urine samples. The approach was essentially a study of the biochemical epidemiology of the two populations and did not involve patients who had developed stones, but rather the population living in endemic and non-endemic bladder stone areas. In Egypt and Pakistan it was not possible to use the Thai approach because the stone cases were not localized in specific areas. For this reason, subjects with overt stone disease who were brought to the hospital for treatment were compared with subjects of the same approximate age but without stone symptoms.

When our studies were undertaken, there were some suggestions that idiopathic bladder stone disease might be a result of some form of malnutrition, although the specific nutrients involved had not been identified. The suggestions were made primarily on the basis of animal studies in which deficiencies of magensium, vitamin

A, phosphate, vitamin $B_6$, protein, etc. resulted in stone formation, and from information about stone disease in children which indicated that it was a disease of the poor who showed signs of several deficiency diseases.

The major finding of our investigations is that inorganic phosphate deficiency appears to be one of the etiological factors in urinary bladder stone disease in children. This suggestion is based upon the following observations:

- Thai village children living in endemic stone areas excrete considerably less inorganic phosphate than their counterparts living in urban, non-endemic areas.
- Egyptian children with bladder stone disease excrete low levels of inorganic phosphate which are about equivalent to or less than Thai village children.
- Pakistani children with stone disease excrete less inorganic phosphate than control subjects of approximately the same age but without stones.

An observation made in the Thai investigations and confirmed in the Egyptian and Pakistani studies was that oxalcrystalluria was common in children living in endemic stone areas and in children with overt stones. We concluded that crystalluria was a fore-runner of stone disease and could be used as a warning sign of pending difficulties. The following observations are pertinent:

- Thai village children living in endemic stone areas frequently showed oxalcrystalluria, uric acid crystalluria, and sometimes phosphate crystalluria whereas children living in urban, non-stone areas seldom showed crystalluria.
- Essentially all Egyptian children admitted to the hospital for bladder stone disease demonstrated crystal formation in their casual and 24-hour urine samples.
- Several forms of crystalluria were found in Pakistani children admitted to hospitals for bladder stone disease.

In Thailand, Egypt, and Pakistan, the crystalluria observed in subjects could be reduced or entirely eliminated by the administration of oral supplements of inorganic orthophosphate salts. This latter observation is of great significance and provides further evidence that a phosphate deficiency was a contributing factor in crystalluria and probably to eventual stone disease.

A number of factors may contribute to the formation of stones in the urinary tract. Our investigations contributed in the following areas:

- infant feeding practices may contribute to bladder stone disease by the substitution of foods of low nutritional quality for breast milk.
- recurrent episodes of diarrhea or fever may contribute to mild dehydration which could result in transient changes in urine composition.
- ingestion of foods containing high levels of oxalate could increase the intensity of oxalcrystalluria.
- ingestion of hydroxproline, a precursor of oxalate in the mammalian body, resulted in greater oxalcrystalluria, larger crystals, and a change in crystal form from octahedral to dumbell shape. Foods which contain hydroxyproline (gelatin) may contribute to stone disease.

A field trial was initiated in Thailand to test the hypothesis that inorganic orthophosphate supplements would prevent bladder stone disease and its presumptive symptoms in children. Approximately 500 children of age 6 months to 6 years were given daily supplements of phosphate salts at a level of 30-60 mg phosphorus per Kg of body weight. An equal number of children were given a placebo. While the results of these trials are not yet completely available, the following observations have been made:

- the phosphate supplements showed no harmful effects in regard to height, weight, plasma calcium, plasma alkaline phosphatase, and general appearance.
- fewer children receiving the supplement showed severe oxalcrystalluria.

- boys showed oxalcrystalluria more frequently than girls which we consider is due to environmental rather than physiological factors.
- crystalluria was not completely eliminated in subjects receiving phosphate but the crystals observed were smaller with fewer clumps. In earlier studies complete elimination of crystalluria was observed in children under 2 years of age, but in the field trial children up to 6 years of age were studied and this may have affected the results.

Project II. Laboratory Investigations

During the course of the contract period a number of laboratory studies were conducted on subjects related to the clinical investigations on stone disease. Investigations included work on factors affecting oxalate and uric acid excretion in experimental animals, factors affecting the solubility of oxalate and uric acid, and the development of a method for oxalate determination in biological solutions. The following summarizes the main findings:

- Stones were produced in rats fed a low phosphate diet. The stones contained approximately 15% calcium oxalate with the major constituent calcium citrate.
- The low phosphate diet resulted in higher excretion of calcium and oxalate, but lower excretion of phosphate and pyrophosphate compared to normal phosphate diets. These findings are consistent with the excretion pattern found in Thai village children where stones are common.
- Urinary mucopolysaccharides tended to reduce the solubility of uric acid in an in vitro system.
- A GLC method for the determination of oxalate was developed. The method is rapid and accurate and can be used for the determination of urinary oxalate.
- Pseudomonas aeruginosa and Klebsiella pneumoniae, two organisms which can cause urinary tract infections, were found to destroy creatinine in synthetic media containing no added nitrogen. The studies suggest that urinary creati-

nine levels may be affected by some infections.

- Proteins of low biological value do not appear to result in increased uric acid excretion in rats. The nitrogen from these proteins must be lost in urine in other forms.

(b) Index of technical reports:

1. Chulkaratana, S., Van Reen, R., and Valyasevi, A., Studies of bladder stone disease in Thailand. XV. Factors affecting the solubility of calcium oxalate. Investigative Urology Vol. 9, No. 3, 240-253 (1971).

2. Valyasevi, A., Dhanamitta, S., and Van Reen, R., Studies of bladder stone disease in Thailand. XVI. Effect of 4-hydroxy-L-proline and orthophosphate supplementations on urinary composition and crystalluria. AM. J. Clin. Nutr. 26, 1207-1211 (1973).

3. Loutfi, A., Van Reen, R., Abdel-Hamid, G., Mansour, N.S., and Waslein, C., Studies of bladder stone disease in Egyptian children. I through VII. J. Egyptian Med. Assoc. 57, 89-136 (1974).

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(c) Index of all publications issued under this contract:

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13. Sirivech, S., Dhanamitta, S., and Van Reen, R. Effect of level of protein intake on urinary uric acid excretion and serum uric acid. Nutr. Rpts. Internat'l. 17: 349-355 (1978).

14. Van Reen, R., Hilke, A. D., Dhanamitta, S., and Sirivech, S. Urinary uric acid levels in Thai children. Fed. Proc. 37: 400 (1978).

(d) Conclusions drawn from the research:

The results of the studies clearly indicate that urinary bladder stone in children is a disease which is related to the nutritional status of the patients. Phosphate deficiency appears to be one of the major etiological factors, although other factors such as dehydration, ingestion of oxalate, and the ingestion of hydroxyproline may contribute to the disease.

It was concluded that children who obtain their phosphate from plant sources, as in the case in most developing countries, run a high risk of developing bladder stone disease because much of the phosphate ingested is unavailable being in the form of phytate. Children obtaining phosphate from animals or other available sources would have a reduced risk of developing stones.

(e) List of major accomplishments:

It is felt that the following were accomplished:

- phosphate deficiency was identified as one of the etiological factors in

urinary bladder stone disease.

- oxalcrystalluria appears to be a fore-runner of stone disease and almost always accompanies the occurrence of bladder stones.
- phosphate supplements over a prolonged period of time can reduce the occurrence of oxalcrystalluria.
- a GLC method for the determination of oxalate is rapid and accurate and can be used for the determination of oxalate in urine samples.

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