MOLECULAR ASPECTS OF MEDICINE

VOLUME 7

Edited by

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MOLECULAR ASPECTS OF IDIOPATHIC UROLITHIASIS

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Introduction

Calculosis occurs in the salivary, biliary or renal systems, but its importance in biliary and urinary tract is emphasized by a higher frequency at these sites and the serious functional implications associated with the formation of stone. The urinary stones may be lodged in any part of the urinary system, namely, kidneys, ureters, bladder and urethra.

Urolithiasis is documented as one of the oldest diseases afflicting mankind yet its prevalence as an "epidemic" on our planet is still so alarming that "stone belt regions" and "pockets" have been mapped (Gershoff, 1964; Colabawalla, 1971) and it continues to pose a universal health problem. The aspects of a changing pattern of geographical distribution of urinary calculi from the lower urinary tract (bladder, ureters) to the upper (kidneys) is fascinating. The incidence of vesical calculi is relatively rare in some highly developed countries of North America, Great Britain and Western Europe (where prior to the 19th century it was unusually high). This is attributed to the improved nutrition status in childhood and raised standards of living. However, this apparent predominance of renal and ureteric calculi may also reflect the more accurate and sophisticated present-day techniques of dignosis, whereby even the unobstructive nonsymptomatic stone does not miss detection.

In the modern era childhood bladder stone disease is quite common in the still developing Far and Middle Eastern countries lying in a broad belt from North Africa to Syria, Iran, Pakistan, India, Burma, Thailand and Indonesia (Van Reen, 1981).

The age-old adage that urolithiasis is a curse both of affluence and deprivation, is paradoxically true. The many theories for stone formation proposed over the years have lacked scientific investigation until the past century, and no single causative factor could be attributed, due to the enumerable variable factors, like diet, water-supply and climate etc.

Only 10-20% of the calculous patients have a predisposing disease entity, viz. anatomical defect, metabolic or genetic disorder, renal or bowel disease, etc. All others who develop stone for no metabolic obstructive or other underlying pathology are termed as "idiopathic stone formers". It is rather distressing that the pathogenesis and therapy of this malady have remained so elusive.

If the continuing process of a changing pattern in the incidence of stone persists, one may anticipate a gradual disappearance of endemic stones in the developing countries, without the aetiology being determined. As this will take an invariably long time active measures to shorten this period are necessary to delineate the causative factors of this disease. While cystine, uric acid and magnesium ammonium phosphate stones may be difficult to manage, these do not pose a major scientific and therapeutic problem as their incidence is very much lower than calcium stones, which comprise approximately 98% of all urinary calculi. In fact, the pathogenesis of calcium stones is poorly understood and difficult to manage, and poses a universal problem.

The question of why only some members in a family form urinary calculi and how to treat such patients has been a challenge to the clinician since the annals of medicine began. The present review is an attempt to explore within a reasonable encompass: (1) a logical up to-date account of the latest theories, (2) the ever-increasing number of causative factors, being added with newer sophisticated facilities for investigation, and (3) to delineate the various environmental factors and possible derangements in the molecular mechanisms involved in idiopathic urolithiasis. Considerable judgement has been exercised by the authors while compiling data from reports of leading scientists, review articles, and research symposia so as to give a world-wide coverage of current research on urinary lithiasis.

Chapter 1

Epidemiology and Etiology of Idiopathic Stone Disease

1.1. Epidemiology of Bladder Stone Disease

Idiopathic bladder stone disease is a term indicating a condition in which there is an absence of any known local predisposing cause in the bladder itself or of any other predisposing factors, viz. endocrine, or primary infection, or prolonged restricted mobilization (Valyasevi and Dhanamitta, 1977). As reported from many countries, this disease is one of the oldest maladies of mankind, predominantly occurring in children. The earlier medical literature of the late 19th and early 20th centuries from U.S.A., Western Europe and Great Britain, mention idiopathic vesical lithiasis, particularly in young children. The actual occurrence rates are not known because of lack of precise data both about the population at risk and about those admitted to the hospitals. Andersen (1962) reviewed the situation in Europe and found that bladder stones were equally common in children and adults. The frequency of occurrence was highest in Norfolk and Norwich Hospital in England. The occurrence of bladder stones during the different periods from 1871 to 1947 in this area (Fig.1) showed a disappearance of bladder stones in children by 1938 and a simultaneous reduction in the adults (Ridley, 1949).

Shaw (1970) implicated the poverty of Norfolk agricultural workers and defective diet as the etiologic factors of bladder stone disease. Halstead (1981) observed that due to a high rate of deaths of mothers during childbirth and a large number of mothers working in factories, their babies were fed "pap", a liquid preparation made from a variety of cereals. One physician also pointed out that the Norfolk diet, besides having a shortage of milk, contained very little cheese, bacon and fats, and was comprised largely of cereal products.

Though bladder stone disease has gradually disappeared in the developed countries, it still continues to be a major problem in many of the developing countries including Turkey, Pakistan, India, Thailand and Indonesia, due to lack of a nutritionally balanced diet.

1.1.1. Incidence

As early as 1931, McCarrison and others found a bladder stone problem in Southern China and Northwest India. They also noted that the incidence was high in Northern parts and very low in Southern parts of India. Contrary reports (Varalakshmi *et al.*, 1976; Marickar *et al.*, 1977) have indicated that quite a significant population of Kerala and Tamilnadu in Southern India is afflicted with stone disease. Other

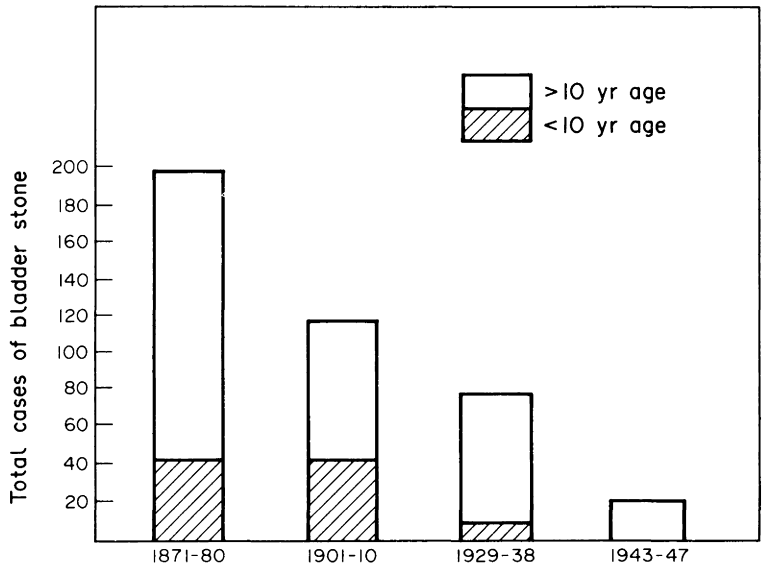

Fig. 1. Bladder stones in Norfolk. From Ridley (1949). Reproduced with permission from *Br.J. Urol.*, 21, 20-23, E & S Livingstone, London.

studies have shown that it also exists in Laos (Westermeyer, 1971), Northern Thailand (Halstead and Valyasevi, 1967), the Middle East and Egypt (Levy and Falk, 1957; Hedayat *et al.*, 1969; Stark, 1970; Loutfi *et al.*, 1974), Turkey (Eckstein, 1961) and Indonesia (Kamardi *et al.*, 1981).

The incidence of stones in different countries and regions during different periods has been compared by Andersen (1969). He divided his studies in three areas: (i) developing countries of S.E. Asia represented by India and Thailand (Fig. 2), (ii) modern industrialized countries represented by Norway and Great Britain (Fig. 3), (iii) countries with an intermediate development along the Mediterranean Sea, e.g. Sicily, Israel, Egypt (Fig. 4). These are contrasted with an area of special interest where stones are very rare among the Bantus of South Africa (Fig. 5). The comparison of pattern is based on hospital incidence, per 10,000 admissions, for lower urinary tract stones in children and adults.

Although bladder stone disease is known to occur in many countries, the epidemiology of the disease within each country is not very well studied. An exception to this is Thailand, which has perhaps the highest incidence of vesical lithiasis in the world. The extensive studies by Halstead and Valyasevi during the period 1963 to 1965 provide a fairly detailed distribution of the disease throughout the country. Hospitalization rate was reported to occur at the frequency of 15 or more per 10,000 residents in North-East and Northern Thailand which are considered to be the endemic bladder stone areas. In India, preliminary studies were aimed at obtaining the pattern of incidence of stone disease, by Andersen (1969) and Colabawalla (1971), which demarcated the two stone belts in India. One belt starts from Amritsar in the North extending to areas in the North-West including Delhi, Agra and ending in U.P. (Uttar Pradesh), while the other belt starts on the west coast at Jamnagar and extends inwards to Central India to Jabalpur. The localities covered in the East and the South show a low index as shown in the map (Fig. 6). Halstead (1961) observed that the rural people were more afflicted than the city or town people in Northern Thailand, whereas only a little difference was noted in rural and urban areas of India (Aurora *et al.*, 1970). It is interesting to note

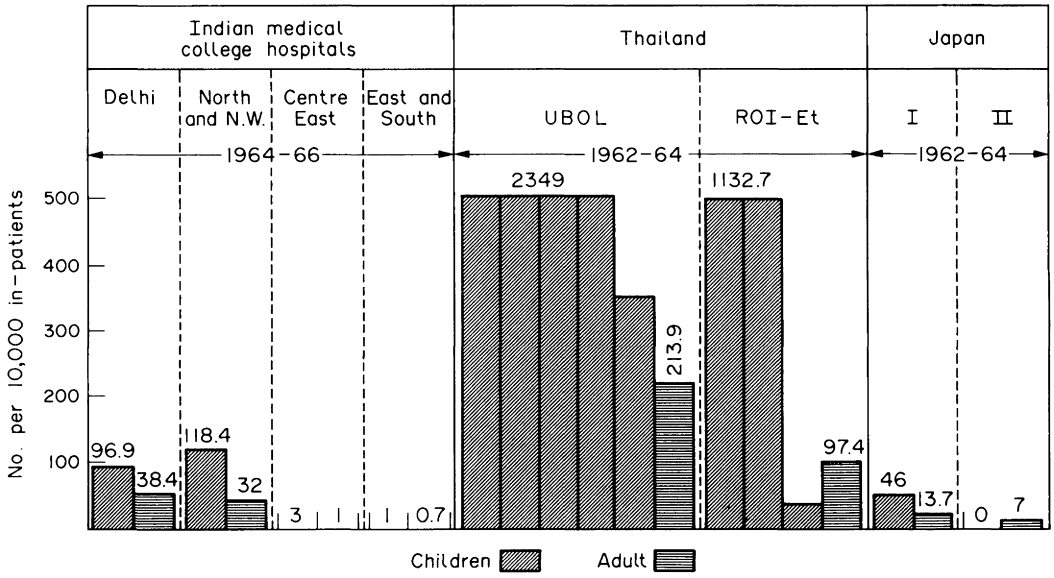

Fig. 2. Histogram of S.E. Asia - India and Thailand. From Andersen (1969). Reproduced with permission from *Proceedings of the Renal Stone Research Symposium*, A. Hodgkinson and B.E.C. Nordin (Eds), J & A Churchill, London.

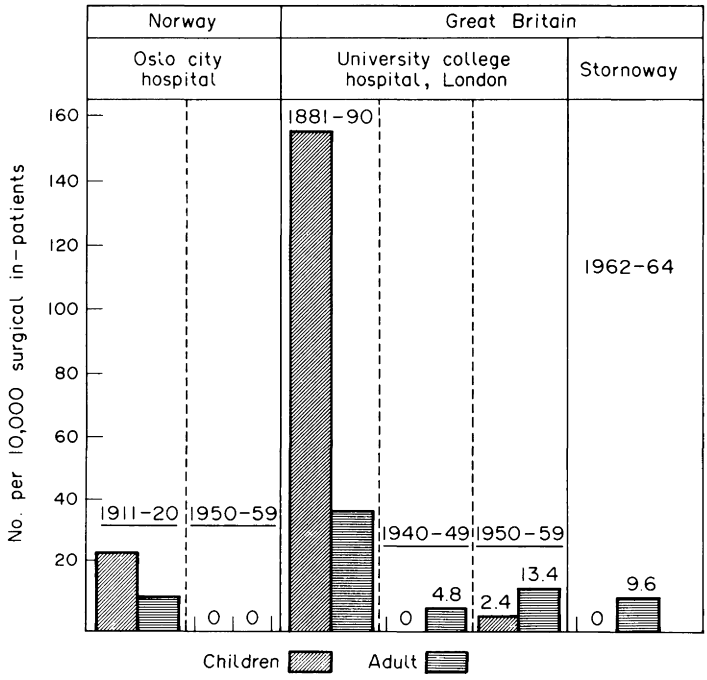

Fig. 3. Histogram of Norway and Great Britain. From Andersen (1969). Reproduced with permission from *Proceedings of the Renal Stone Research Symposium*, A. Hodgkinson and B.E.C. Nordin (Eds), J & A Churchill, London.

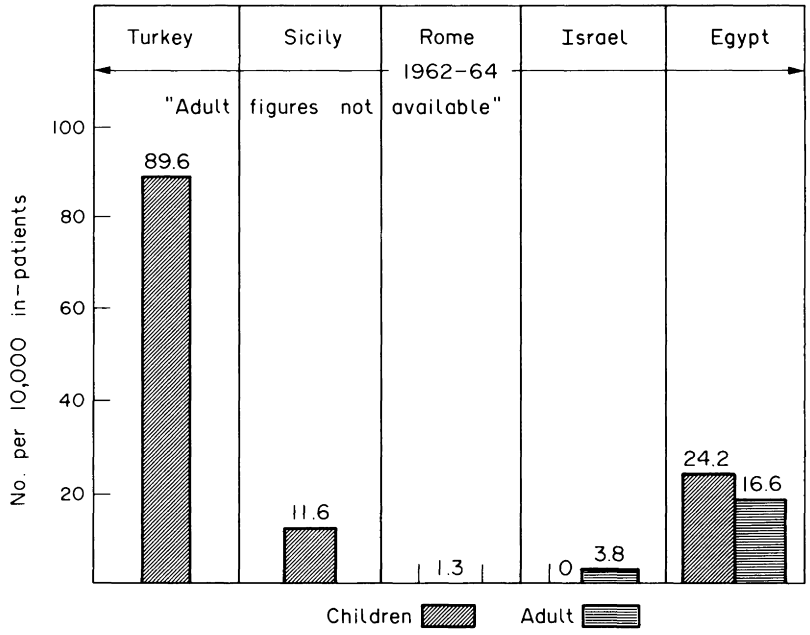

Fig. 4. Histogram of Southern Europe and Mediterranean. From Andersen (1969). Reproduced with permission from *Proceedings of the Renal Stone Research Symposium*, A. Hodgkinson and B.E.C. Nordin (Eds), J & A Churhchill, London.

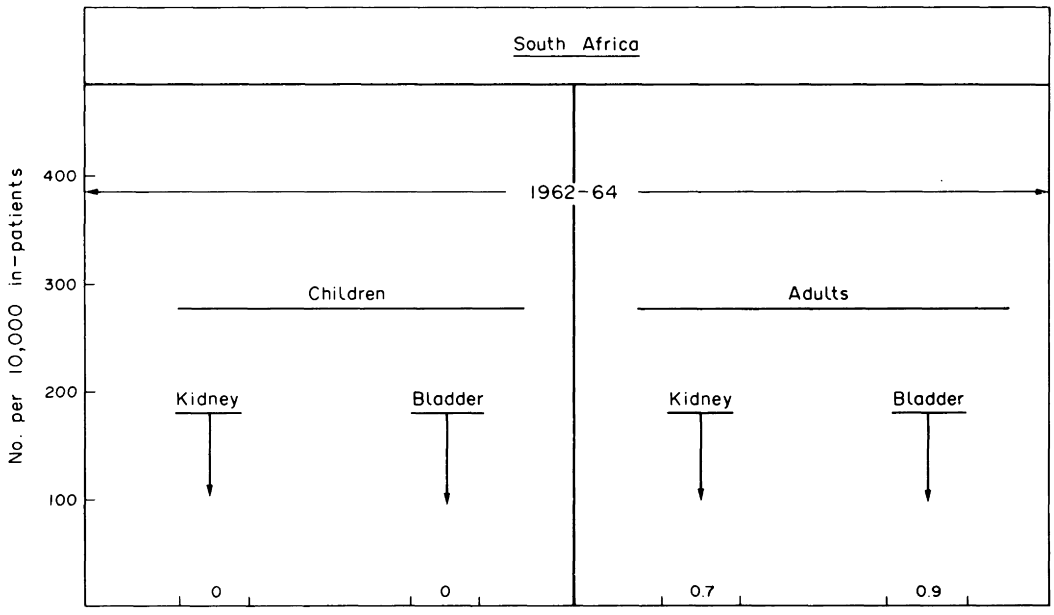

Fig. 5. Histogram of South Africa - Bantu. From Andersen (1969). Reproduced with permission from *Proceedings of the Renal Stone Research Symposium*, A. Hodgkinson and B.E.C. Nordin, (Eds), J & A Churchill, London.

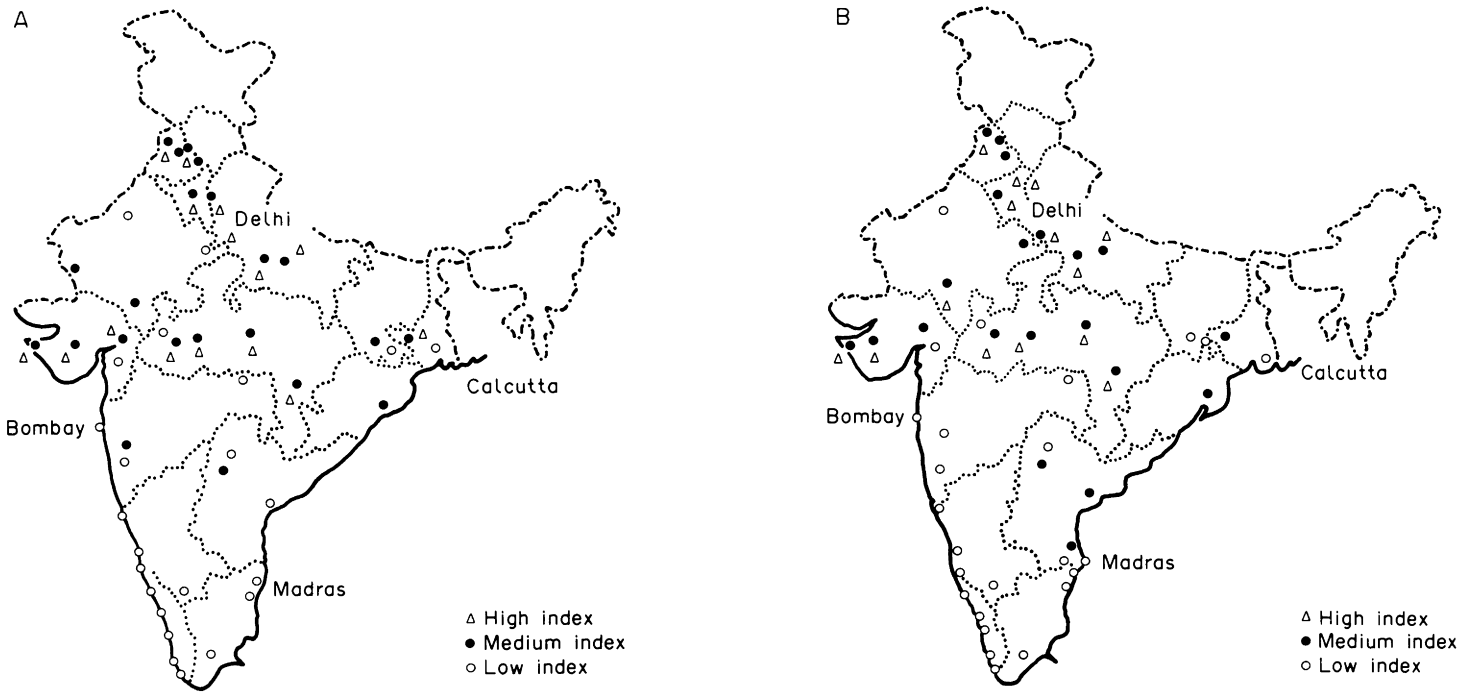

Fig. 6. (A) Patterns of upper tract calculi. (B) Patterns of lower tract calculi. From Colabawalla (1971). Reproduced from *Technical Report Series No.8.*, Indian Council of Medical Research, New Delhi.

that in Egypt the urban children are more afflicted (Loutfi *et al.*, 1974). These studies reveal that geographic and domestic locations have some role to play in the etiology of this disease.

1.1.2. Age and Sex Ratio

Halstead and Valyasevi (1967) noted the peak age of this disease in Thailand to be during the first five years of infant life. About ten males are afflicted for every female showing its predominance in male children. These observations are also confirmed by various other workers (Andersen, 1962; Kabra *et al.*, 1972; Kamardi *et al.*, 1981; Rahman and Van Reen, 1981). Contrarily, there is a solitary report from India showing the absence of bladder stone in children below twelve years of age (Marickar *et al.*, 1977).

1.1.3. Season of Occurrence

The effect of seasonal variation on the frequency of occurrence of this disease is available from the endemic areas of Thailand (Halstead and Valyasevi, 1967). They reported a high occurrence during hot dry weather, somewhat lower values during rainy season and a second peak in November just after the rains ceased (Fig. 7).

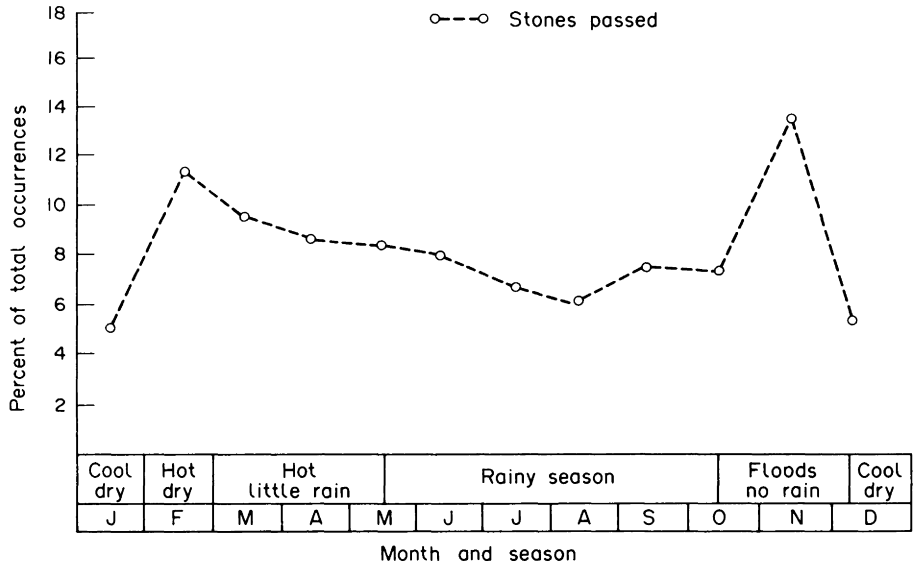

Fig. 7. Percent distribution of month of onset of stone passing episodes in 725 individuals, Ubol Survey (1963). From Halstead and Valyasevi (1967), *Am.J. clin. Nutr.*, 20, 1320-1339.

1.1.4. Ethnic and Socio-Economic Status

Halstead (1961) observed that Chinese communities within the endemic areas of Northern Thailand, and the tribal communities in Manipur State in India (Singh *et*

al., 1978) were least affected. Though the communities of different ethnic origin in such areas are striving to maintain their identity and customs intact, wide differences in domestic habits and life style are noted. In Israel, Levy and Falk (1957) and Stark (1970) observed that Arab and Jewish children of Asian and African origins were afflicted with bladder stone disease, but it was rare among the children of Western Jews, suggesting an environmental accompaniment of poverty as a casual factor. Dupreez and Cremin (1973) noted that in Southern Africa both the children of the affluent White section of the community and the Bantu children from the poorest section were spared, whereas the children of the Cape Coloured community belonging to medium economic status were affected. The low index of bladder stone problem in South and East India (McCarrison, 1931; Anderson, 1969; Colabawalla, 1971) and absence in Greater Africa (McLaren, 1963) areas which are as poor as the endemic stone areas provides further epidemiological evidence that a poor socio-economic environment is not a direct etiological factor.

The epidemiological surveys of bladder stone problem from various parts of the world show that geographical, ethnic and socio-economic are not the only factors in its etiology and indicate the probability of an environmental nutritional factor involving both the expectant mother and the child and exerting its influence during a finite period in the life of an infant.

Detailed investigations of the domestic and dietary habits, and biochemical features of blood and urine of Thailand, Turkey and Egypt (Eckstein, 1961; Valyasevi and Dhanamitta, 1967; Valyasevi *et al.*, 1967a; Chulkaratana *et al.*, 1971; Valyasevi *et al.*, 1973; Loutfi *et al.*, 1974) have revealed that the children in affected areas manifest hyperoxaluria, and have lower urinary inorganic phosphate, pH and osmolality than the children from unaffected areas. The oxalate precursor hydroxyproline was found to exacerbate oxalate crystalluria already present, while the administration of orthophosphate reduced both this and crystal aggregation. Crystal solubility was also increased by citrate, magnesium, pyrophosphate and phosphonates.

1.1.5. Composition of Bladder Stone

A knowledge of chemical composition of urinary calculi helps in understanding the pathogenesis of its formation. Simple chemical methods though informative do not give the exact chemical nature of the stone. More sophisticated methods viz. optical crystallography, X-ray diffraction and infrared spectroscopy are employed, where available, to reveal the exact chemical nature of the stone. A number of reports of simple chemical analysis in India from Ahmedabad (Parikh and Shah, 1960), Ahmednagar (Andersen *et al.*, 1963), Gwalior (Rao *et al.*, 1964), Chandigarh (Thind and Nath, 1969), Delhi (Malhotra *et al.*, 1968) and Meerut (Teotia and Teotia, 1977) revealed that ammonium acid urates in combination with calcium and oxalate, made a significant percentage of the stone. The chemical analysis, as well as X-ray diffraction analysis, of bladder stones in Thailand shows that these are composed mainly of calcium oxalate, ammonium urate, calcium phosphate, uric acid and uric acid dihydrate (Sakornomonkal and Dhanamitta, 1962; Gershoff *et al.*, 1963; Sootajt and Phorphibul, 1963; and Lonsdale and Mason, 1966). Results of simple chemical analysis and X-ray diffraction study of bladder calculi collected from endemic areas of Rajasthan in India by Gaur *et al.* (1972) showed that the vesical stones are comprised of calcium oxalate, ammonium acid urate, calcium phosphate, uric acid and magnesium ammonium phosphate (Table 1).

Table 1. Comparison of the percentage occurrence of various components in bladder stone from India with those from other countries using X-ray crystallographic technique (%age occurrence of various components)

Series	Number of stones analysed	UAA	UAD	AAU	COM	COD	CYS	COA	GYA	BRT	MAPH	SAU
England												
Lonsdale *et al.* (1968)	53	49.0	8.0	77.0	85.0	30.0	-	15.0	13.0	8.0	23.0	-
India												
(a) Lonsdale *et al.* (1968)	46	31.0	7.0	89.0	98.0	67.0	-	-	9.0	-	29.0	4.0
(b) Rao *et al.* (1970)	30	16.7	3.3	73.3	73.3	20.0	-	36.6	3.3	3.3	16.7	-
(c) Gaur *et al.* (1972) (only S.E. Rajasthan)	44	32.0	-	77.2	93.1	45.0	-	18.1	13.6	-	36.6	2.2
(d) Ghori *et al.* (1982) (only Meerut region)	16	-	-	45.0	80.0	13.0	-	-	-	-	13.0	-
Thailand												
(a) Gershoff *et al.* (1963)	200	18.0	-	76.0	76.0	-	-	-	-	-	15.0	-
(b) Lonsdale *et al.* (1968)	58	12.0	9.0	95.0	90.0	88.0	-	12.0	2.0	-	10.0	2.0

UAA - Uric acid anhydrous; UAD - Uric acid dihydrate; AAU - Ammonium acid urate;
COM - Calcium oxalate monohydrate; COD - Calcium oxalate dihydrate; CYS - Cystine;
COA - Carbonate apatite; HYA - Hydroxyapatite; BRT - Brushite;
MAPH - Magnesium ammonium phosphate hexahydrate; SAU - Sodium acid urate

Valyasevi and Van Reen (1968) observed some similarities in those areas where the disease is endemic in children, which are as follows:

(1) It occurs predominantly in children under 10 years of age.

(2) The rate of hospital admissions is higher for boys than in girls.

(3) The stones are usually composed of calcium oxalate and ammonium acid urate.

(4) The rate of recurrence following the surgical removal is low in comparison to renal lithiasis in adults.

(5) The disease is generally prevalent among the children in low economic class.

1.2. Etiology of Bladder Stone Disease

The etiology factors responsible for the bladder stone disease in various countries are supposed to be dietary habit and nutrition.

1.2.1. Nutrition Factors and Urolithiasis

Van Reen has studied the relationship between urolithiasis and nutrition in animal models and made the following observations (WHO Regional Symposium, 1972):

(1) Rats fed on vitamin A deficient diets developed renal and bladder calculi. It was postulated that a calculus is formed due to the degeneration of urinary tract epithelium.

(2) Magnesium deficiency resulted in nephrocalcinosis. The mechanism suggested is an increase in parathyroid gland activity resulting in hypercalcaemia.

(3) Inorganic phosphate is another nutrient that is related to stone formation. Rats fed on a low phosphorus diet formed calcium citrate stones. However, in weanling male rats, a moderately low phosphorus diet resulted in a high incidence of bladder lithiasis, of which more were of the calcium oxalate type than calcium citrate. It is of special interest that calcium oxalate is predominant in human bladder stones. Oxalcrystalluria and low urinary phosphorus are commonly found in the urines of stone patients. The relationship between the two is not clearly understood.

(4) Low protein diets resulted primarily in calcium citrate stones in the bladder due to alkalinization of urine. Addition of protein, methionine or sulfate to the diet resulted in acidification of the urine and elimination of stones.

(5) Vitamin B_6 deficient diet fed to cats showed oxalate nephrocalcinosis along with increased urinary oxalate and decreased urinary citrate excretion. Feeding magnesium to vitamin B_6 deficient rats caused a marked reduction in renal oxalate deposits while the high oxalate excretion remained unaffected, suggesting that magnesium supplementation increases the solubility of calcium oxalate.

Some of the data obtained from the animal experiments especially with low phosphate diets, are relevant to the clinical studies in Thailand.

1.2.2. Relationship Between Dietary Habits and Bladder Stone Disease

Comparative studies (Valyasevi *et al.*, 1967b; Halstead *et al.*, 1967; Valyasevi and Dhanamitta, 1967) made of the dietary habits of village (endemic stone area) and city (non-endemic) dwellers revealed the following salient features.

1.2.2.1. Infant feeding practices (Valyasevi *et al.*, 1967b). These differed markedly among the families living in villages and cities. About 60% of the village mothers started their infants on "glutinous rice" feeding during the first week of life and about 85% during the first month. The amount of rice ranged from 47 to 60 g per day which supplied about 50-60 calories/kg body weight/day. On the other hand, the city mothers did not start feeding rice until the child was three months old. Families feeding their infants rice during the first week had twice the prevalent rate of bladder stone disease as compared to those supplementing it later, explaining the high frequency in this population having a history of early rice feeding.

McCarrison (1931) in India has shown that whole wheat flour and South Indian millet have the highest and lowest stone producing potencies, respectively. Teotia and Teotia (1976) studied the correlation of the dietary pattern with incidence of bladder stone disease in the Indian subcontinent and revealed that it occurred more frequently in the areas where the staple food had been wheat. Their short term experimental results have conclusively shown that whole wheat flour, when consumed as staple food, leads to the production of urine supersaturated with uric acid, an essential prerequisite for bladder stone formation (Teotia *et al.*, 1981). They have suggested that the substitution of rice for wheat in endemic bladder stone areas may be useful in the prevention of bladder stone disease in children.

The significance of the presence of a high content of ammonium acid urate in the stone obtained from Indonesian children was studied by Brockis *et al.* (1981), who observed a high ammonium ion concentration in the infants' urine in areas where dietary phosphate is lacking. It is associated with aciduria, induced by a wheat or rice flour diet. They have suggested that the amount of basic phosphate available is not enough to buffer the acidogenic effect of the diet.

Andersen (1972) observed that the bladder stone among the poor children in Sicily disappeared rapidly following general protein supplementation in their diet. He indicated that this may be due to improvement in maternal nutrition during pregnancy and lactation, as well as the direct effect of the availability of milk products for infant feeding. Thomas (1949) also observed the disappearance of bladder stone in Norfolk with the introduction of dairy farming and greater prosperity; paradoxically other communities on a low protein diet, did not have bladder stone. It has been suggested that the early substitute feeding of infants with the feeds which are predominantly carbohydrate is a critical factor.

Low protein diet undoubtedly accounts for low urinary content of phosphate, whereas predominantly feeding carbohydrate results in low urinary pH leading to a reduced urinary citrate excretion. Others (Smith and Woodruff, 1951; Lennon *et al.*, 1968), found that both these severe dietary condtions may lead to acidosis.

Currently the attention is directed towards the significance of uromucoproteins in the etiology of stone formation. It is believed that stone matrix is derived from urinary mucoproteins. A special type of uromucoid may exist in the urine of stone formers which may contribute to the initiation of nucleus formation.

Studies on urinary mucoproteins in newborn infants of hyper-(rural) and hypo-(urban) endemic areas of Thailand (Dhanamitta *et al.*, 1970) showed that village

newborns excreted a significantly higher amount of total non-dialyzable solids than the urban group, which contained a significantly lower percentage of the 1,000-5,000 MW fraction and higher of the 5,000 MW fraction. The reason for these differences and the significance of these findings are not clear, though it is speculated that these may be contributing factors to the occurrence of bladder stone disease. On the basis of various etiological factors, Valyasevi and Dhanamitta (1977) proposed a hypothesis of bladder stone formation in Thailand (Fig. 8).

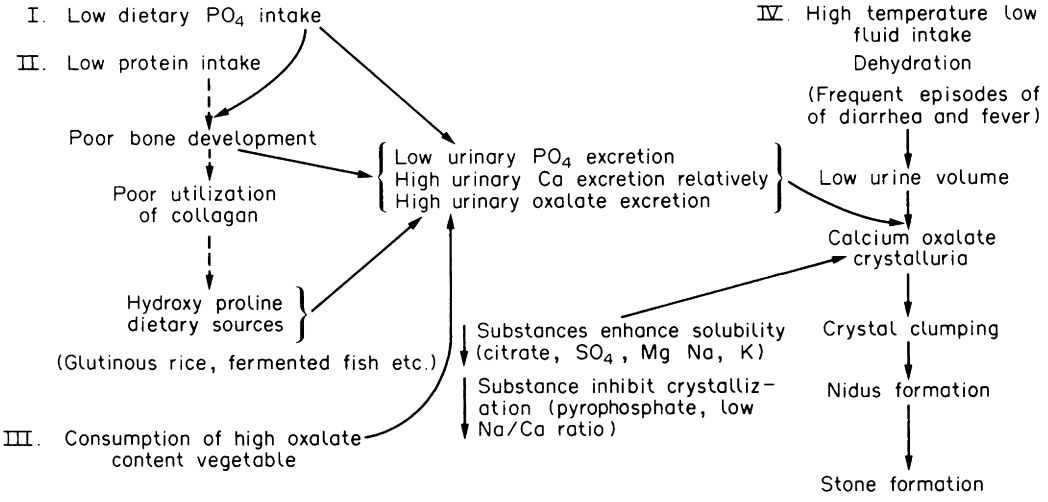

Fig. 8. Hypothesis of bladder stone formation in Thailand. From Valyasevi and Dhanamitta (1977), Proceedings International Symposium on Idiopathic Urinary Bladder Stone Disease.

1.2.2.2. Orthophosphate supplementation. It is generally observed that the children in the endemic stone areas of Thailand excrete low amount of urinary phosphate. It is believed that low urinary phosphate excretion could be due to low dietary intake, poor intestinal absorption or other factors.

Effect of orthophosphate supplementation on the bladder stone disease in Thailand has been extensively investigated (Dhanamitta *et al.*, 1967; Valyasevi *et al.*, 1969). Orthophosphate was supplemented to the children in addition to their usual regimen of breast-feeding and premasticated glutinous rice. The microscopic examination of urine revealed the disappearance of crystalluria. In addition to this there was a marked increase in total urinary phosphate and pyrophosphate and at the same time urinary calcium and oxalate excretions decreased markedly. The urinary uric acid excretion was not changed but the increase in urine pH may be partly responsible for the decrease in uric acid crystals. The mechanism by which oxalic acid excretion is reduced during the oral orthophosphate supplementation is still not clear.

Fleisch and Bisaz (1964a,b) have indicated that pyrophosphate inhibits both hydroxyapatite and calcium oxalate precipitation. Therefore, oral administration of the phosphate, producing elevated levels of pyrophosphate in the urine of children, may be a factor in preventing the crystalluria. It was also demonstrated that urinary citric acid increased significantly during the orthophosphate supplementation, which was related to increase in urinary pH resulting from the phosphate administration. Citric acid can chelate with calcium and therefore could influence the formation of calcium oxalate crystals.

1.3. Epidemiology of Renal Stone Disease

Andersen (1972) described two separate factors involved in the genesis of renal lithiasis. These are known as intrinsic and extrinsic factors. Intrinsic factors include heredity, age and sex, ethnic, racial, familial background as well as any inherited physiologic or anatomic predispostion to urinary calculi. Extrinsic factors include geographical pattern, climate, availability of drinking water, dietary habits of populations and of households having people with urinary calculi, the presence or absence of trace elements in food stuff and drinking water and different occupations. Several reviews dealing with intrinsic and extrinsic factors have been consulted for the discussion in this section.

1.3.1. Intrinsic Factors

1.3.1.1. Heredity. Numerous reports have indicated that urinary calculi are rare in North American Indians, the Negroes of Africa and America and the natives of Israel. Resistance to urinary stone disease among these individuals may be related to heredity. Although the incidence of bladder stones appear to be related to dietary habits and malnutrition in under-developed and primitive countries, improvement in diet due to awareness and industrial development over the years have changed the site of occurrence of stone from bladder to kidney (Sutor, 1972). In other words, the hereditary capability of forming stones persists while the anatomic site of formation has changed.

Renal tubular acidosis is one of the hereditary diseases associated with frequent episodes of occurrence of urinary stones. Nephrocalcinosis and nephrolithiasis have been manifested in almost 73% of patients with this disease (Dretler *et al.*, 1969). Incomplete renal tubular disease is another hereditary trait which results in urinary calculi formation.

Primary hyperoxaluria, another congenital disorder, is related to enzyme deficiencies resulting in impaired glyoxylate metabolism leading to increased synthesis and excretion of oxalic acid (Williams and Smith, 1968; Hagler and Herman, 1973a,b; Watts, 1977). Type I hyperoxaluria is caused by a genetically determined eficiency of cytoplasmic 2-oxoglutarate-glyoxylate-carboligase in tissues with glycolic and glyoxylic acidurias. Type II primary hyperoxaluria is attributed to inherited deficiency of D-glycerate dehydrogenase (EC 1.1.1.29) causing L-glyceric aciduria and normal glycolate and glyoxylate excretion.

Cystinuria is also a genetic disorder which causes an excessive excretion of cystine, lysine, ornithine and arginine of which only cystine becomes insoluble in urine (Crawhall and Watts, 1968; Watts, 1977).

Lastly, hyperuricosuria is due to four enzyme defects leading to uric acid overproduction. These four enzymes which have been identified (de Vries and Sperling, 1977; Watts, 1977) are: (1) hypoxanthine-guanine phosphoribosyl transferase (EC 2.4.2.8) deficiency (Henderson *et al.* 1976), (2) increased activity of phosphoribosyl phosphate synthetase (EC 2.7.6.1), (de Vries and Sperling, 1973), (3) glucose 6-phosphatase (EC 3.1.3.9) deficiency, and (4) increased activity of glutathione reductase (EC 1.6.4.2). The familial incidence of urinary calculi is also related to the heredity, evidence for which was offered by Goldstein (1951) while the genetic studies have been made by McGeown (1960) and Resnick *et al.* (1968). These workers conclude that urolithiasis requires polygenic defects. Ljunghall and Hedstrand (1975) in a population survey found an association of renal stones in at least first degree relatives in 29.4% of stone patients as compared to 15.3% of stone-free control subjects. But the findings of White *et al.* (1969) in which

increase in calcium excretion was found not only in stone formers but also in their spouses suggest the possibility of a household factor. Hence, the household diet as well as familial tendencies should be considered in the etiology of urinary lithiasis.

1.3.1.2. Age. Idiopathic calcium stone disease is uncommon in children and elderly people and its peak lies within the third to fifth decade of life (Drach, 1978). Several other authors have also pointed to a rapid increase starting from 25-30 years, a peak rise at the age of 50-59 years (Fetter and Zimskind, 1961; Churchill *et al.*, 1979; Ahlstrand and Tiselius, 1981; Hesse *et al.*, 1981). Ghazali *et al.* (1973) have shown that this disease also occurs in childhood. Between the puberty and menopause, the incidence in the female is half that in the male of the same age; this may be due to the effect of estrogens in increasing urinary citrate excretion which has a solubilizing effect on calcium oxalate. Unlike bladder stone disease, idiopathic calcium nephrolithiasis is a recurrent condition and recurrence rates of 75% (Williams, 1963), 67% (Blacklock, 1969) and 72% (Ljunghall and Hedstrand, 1975) have been reported. It has been suggested that high recurrence rates may be related to prolonged exposure to etiological factors.

1.3.1.3. Sex. One of the striking features of idiopathic calcium stone disease is that its incidence is predominant in males rather than females. Several workers have reported that three or four males are afflicted for every female (Inada *et al.*, 1958; Fetter and Zimskind, 1961; Blacklock, 1969; Drach, 1978; Dajani *et al.*, 1981; Ahlstrand and Tiselius, 1981). The reason, as proved by Robertson *et al.* (1968), is that males have a greater urinary excretion of calcium, oxalate and uric acid than females and produce higher saturation levels of calcium oxalate and calcium phosphate.

1.3.2. Extrinsic Factors

1.3.2.1. Geography. Renal stone is common in areas such as Europe, North America and Japan which have high degrees of technical development and relative affluence. It has been observed that in Southern Africa the indigenous Bantus are rarely afflicted with stone disease while living within their tribal environment (Vermooten, 1937; Wise and Kark, 1961), whereas the incidence in the White and Indian populations is as common as it is in Europe and North America. Similarly, the American Negro possessed a similar immunity to renal stone disease (Reaser, 1935), though ten years later Dodson and Clark (1946) and others found an increasing incidence of renal stones in Negroes. This can be correlated to the accomplishment of greater affluence and adoption of a life-style resembling their Caucasian countrymen.

Finlayson (1974) reviewed several world-wide geographic surveys and observed that the United States has a relatively high incidence of urinary calculi. Other high incidence areas are British Isles, Scandinavia, the Mediterranean countries, Northern India and Pakistan, Northern Australia, Central Europe, portions of Malayan peninsula and China. Low incidence areas include Central and South America, most of Africa and those areas of Australia populated by native aborigines.

The incidence of renal stones in various parts of India as reviewed by Colabawalla (1971) shows a more or less similar pattern for both the upper and lower urinary tract stones.

The striking feature in the relationship of hospital admissions, their stone symptoms and country of origin (Wisniewski *et al.*, 1981) is the relatively low incidence in the Australian Aborigines, males and females as compared to other countries and the migrant population of Australia (Tables 2 and 3).

Table 2. Incidence of stone, relating to country of origin (males)

Country	SMR (Standard morbidity rate)	Rate (per 100,000 in the population per year)	Number*
Australia	1.0	71.5	1762
U.K.	1.2	84.0	673
Germany	1.4	98.4	36
Italy	2.4	170.0	277
Greece/Yugoslavia	2.0	147.2	122
Netherlands	1.9	136.8	82
Rest of Europe	1.6	112.4	152
New Zealand	0.8	59.1	19
India	1.6	114.7	54
Rest of Asia	1.0	70.3	58
Rest of World	0.3	19.6	53
Aborigine	0.5	38.5	32

*Number of hospital admissions for stone from 1971 to 1977.
Data from Wisniewski *et al.* (1981). Reproduced with permission from Urinary Calculus, edited by Brockis and Finlayson © 1981 by PSG Publishing Company Inc., Littleton, Massachusetts.

1.3.2.2. Climatic factors. The incidence of urinary calculi has been related (Prince *et al.*, 1956) to high summer temperatures in south-eastern United States, the peak incidence being during July, August and September (Fig. 9) which are the months with the highest average temperatures, as was later confirmed by the same group of workers (Prince and Scardino, 1960).

Batesone (1973) studied the incidence of urinary calculi in the areas surrounding Perth and Western Australia (Fig. 10) and reported a peak incidence from December to March which coincides with months in that hemisphere having maximum temperature. Rivera (1973) reported the seasonal incidence of urinary calculi in the areas surrounding San Juan and Puerto Rico. He observed that maximum incidence of urolithiasis was during July to October in most years, excluding some unexpected seasonal changes which resulted in unusual coolness during periods of relatively