Chapter-1

INTRODUCTION

Calculosis (deposition of ions in the form of calculi) can occur in the salivary, biliary or renal systems, but its importance in urinary tract is emphasized by its high frequency of occurrence and the serious functional implications associated with it. Almost all human beings are known to pass crystals in their urine, however, only 10 percent of the population is known to experience clinical manifestations of stone formation. Stone formation in the urinary tract has been recognized for hundreds of years. The urinary stones may be lodged in any part of the urinary tract namely kidneys, ureters, bladder or urethra.

Until last century, concrements in the lower urinary tract, particularly in the urinary bladder, were known to be the predominant form (Elliot, 1973; Danielson, 1985; Goldwasser et al., 1986). Bladder stone disease, still occurs in the developing countries, however, it has almost been completely eradicated from the western world, perhaps due to their improved standard of living/nutrition (Finlayson, 1974). In contrast to urinary bladder stones, stones in the upper urinary tract have become much more common. It has been shown that the renal stones now-a-days are at least 10 times more common than at the beginning of this century. Renal stones seems to be a disease of affluence. The increased frequency of renal stones has
been attributed to the increased intake of animal proteins (Hodgkinson, 1977; Fellstrom et al., 1983 and Conyers et al., 1985). Geographic variations are also known to occur, but the reasons for these are not very clear (Lonsdale, 1968). Dietary differences and the hardness of water have often been thought to be the contributing factors (Robertson et al., 1975). It has been shown that 10-20 percent of the males and 3.5 percent of the females suffer from renal stone disease (Robertson et al., 1968; Ahlstrand and Tiselius, 1981 and Hesse et al., 1985). It has also been shown that majority of stone formers have recurrences. In 50 percent of cases, at least one recurrence after 4-5 years has been reported (Johnson et al., 1979).

Majority of the renal stones are calcium containing concrements consisting of calcium oxalate, calcium phosphate or mixtures of these salts. A smaller proportion (3-5 percent), the so-called infection-induced stones, consist of magnesium-ammonium-phosphate (Struvite). Least common renal stones are those composed of uric acid or cystine (Herring, 1962; Elliot, 1968; Hodgkinson and Marshall, 1975 and Ottes, 1983).

Although the precise mechanism leading to stone formation is not clearly understood, yet stone problem can primarily be regarded as a physiochemical problem. Since urinary calculi are crystalline in nature, it is logical to assume that the factors which are known to influence the formation and the growth of crystals in nature,
could also be involved in the formation of urinary calculi. According to the classical crystallization theory, the spontaneous crystallization from the solutions does not occur unless the formation product is exceeded and the crystal growth does not occur until solubility product is exceeded. It is thus logical to assume that the factors which can either influence the concentrations of the calculi constituents in the urine or their solubilities may be of considerable importance in the etiology of urinary calculi. Studies (Elliot, 1973 and Robertson et al., 1975) have demonstrated that urine from male kidney stone patients does not differ from that of the normal subjects as far as the concentration of stone forming constituents in the urine was concerned. These studies thus suggested that factor(s) other than concentration of the reactants may be important in the etiology of Urolithiasis.

Howard and Thomas (1958) postulated that factor(s) inhibitory to mineralization, may be present in the urine of normal human beings and that these factors may either be absent or present in lesser concentrations in the urine of stone formers. Further, in order to explain why all our collagenous tissues do not normally get mineralized and turn us into pillar of stones, scientists (Fleisch and Neuman, 1961; Kumar and Jethi, 1975; Smith, 1982; Rose and Sulaiman, 1984a and Martin et al., 1985) have shown that human body fluids contain inhibitors of mineralization
and that these inhibitors may play a possible role in the control of selective tissue mineralization. Although during the past 20 years or so, a lot of work has been done on the chemical nature and the possible role of the inhibitors in the control of physiological and/or pathological mineralization, yet the review of literature reveals that the results are far from conclusive.

In order to assign one or more than one of these biomolecules present in the body fluids a possible role in the control of biological mineralization and/or urolithiasis, it is not only imperative to isolate, purify and characterize these biomolecules from the urine of normal persons and kidney stone patients but also to know whether any differences exist regarding these biomolecules in the urine of normal persons and kidney stone patients. Review of literature revealed that a great controversy exists not only regarding the chemical nature of the physiologically important inhibitors but also whether any differences exist regarding these biomolecules in the urine of normal persons and kidney stone patients.

From time to time scientists have been tempted to assign either one of the cations like Mg$^{2+}$, Mn$^{2+}$, Zn$^{2+}$, Cd$^{2+}$, Cu$^{2+}$, Co$^{2+}$, Fe$^{2+}$, Al$^{3+}$ (Bird and Thomas, 1963; Feagin et al., 1969; Meyer and Thomas, 1982; Blumenthal and Posner, 1984 and Li et al., 1985); anions like HCO$_3^-$, P$_2$O$_7^{4-}$, F$^-$, SiO$_4^{2-}$, CrO$_4^{2-}$, C$_6$H$_5$O$_3^-$ and phosphonates
(Sobel and Burgar, 1954; Bachra, 1967; Pak, 1972; Russell and Fleisch (1973); Schwille et al. (1979) and Meyer, 1984 & 1985); peptides having molecular weight between 500 to 20,000 (Howard et al., 1967; Barker et al., 1970; Ito and Coe, 1977 and Hisao and Hisamitsu, 1981); glycoproteins (Nakagawa et al., 1978, 1981, 1983, 1984 & 1985) or mucopolysaccharides (Gardner and Doremus, 1978; Sallis and Lumky, 1979 and Ryall et al., 1986) a possible role in the control of physiological/pathological mineralization.

Rose and Sulaiman (1984a & b); Robertson et al. (1984) and Scurr and Robertson (1985b) observed that in addition to inhibitors of crystal formation, human urine also contains certain polymeric uromucoids which may act as promoters of crystal formation. One such mucoprotein—Tamm Horsfall, present in human urine has been shown to promote the crystal formation of both calcium oxalate and calcium phosphate.

Regarding the relative differences in the levels of inhibitors/promoters in the urine of normal persons and kidney stone patients, some workers (Robertson et al., 1973; Sutor, 1973; Teotia and Teotia, 1975; Barker et al., 1974; Bauman et al., 1977 and Singla et al., 1978) have clearly demonstrated that as compared to normal persons, kidney stone patients excrete much lower levels of the inhibitors in their urine, however, other workers (Orepoulos et al., 1975 & 1976; and Crassweller et al., 1978) have failed to detect any such quantitative
differences in the urine of normal persons and kidney stone patients.

Although all scientists agree that an organic matrix is always associated with the renal calculi, yet controversy still exists regarding its precise role. According to some workers (Keutal, 1965; Malek, 1977; Rose and Sulaiman, 1984a & b and Scurr and Robertson, 1985b) the organic matrix by acting as a specific nucleator of calcium salts formation is responsible for initiating calculi formation, however, according to other workers (Keutal and King, 1964 and Robertson et al., 1972), the presence of the organic matrix in the calculi is due to a result of secondary adsorption of the matrix on the faces of the growing crystals. In other words controversy also exists whether nucleation is essentially homogeneous or heterogeneous.

Keeping in view the above status of literature, present studies were planned to investigate the following:

1. Effect of whole urine from normal persons and kidney stone patients on the extent of calcium and phosphate precipitation (mineralization) using the homogeneous system of mineral phase formation.

2. Effect of whole urine from normal persons and kidney stone patients on the release of ions from the preformed mineral phase into the aqueous phase (demineralization) using homogeneous system.
3. Isolation and purification of the active biomolecules from the urine of normal persons and kidney stone patients.

4. Effect of whole urine from normal persons and kidney stone patients and the purified biomolecules isolated from their urine samples on the rate and the extent of mineralization and ion exchange reactions, using heterogeneous system of catalysis.