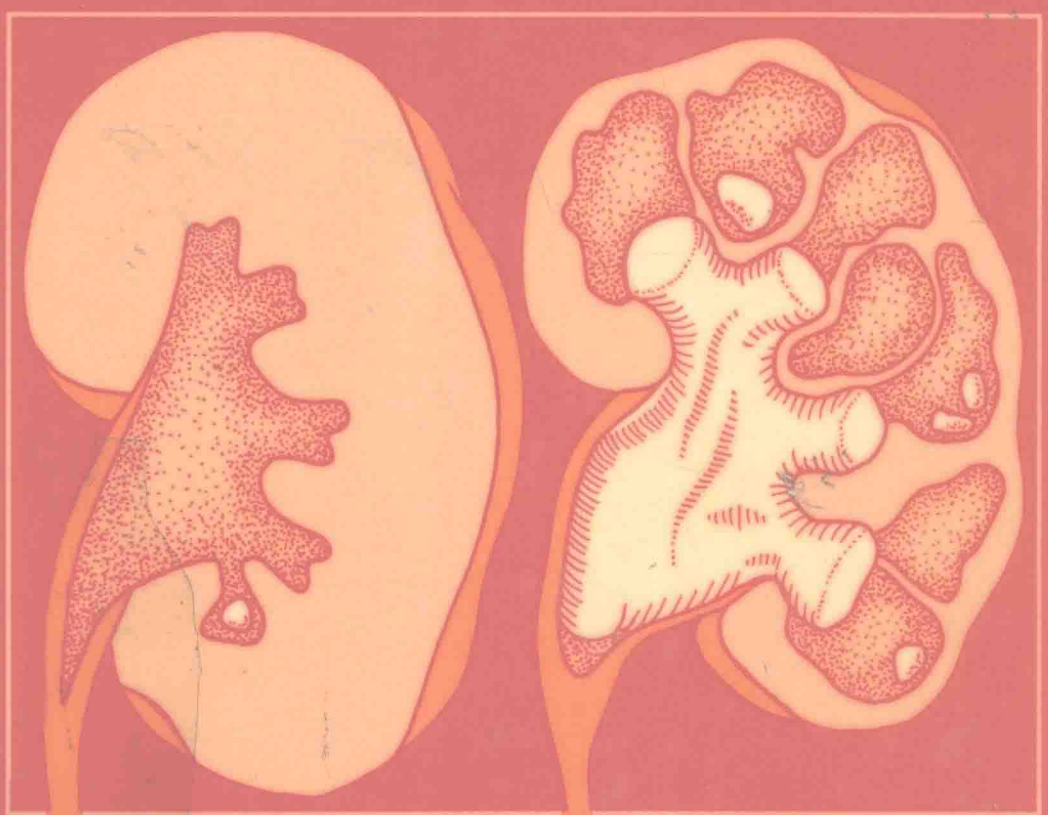
CHURCHILL LIVINGSTONE

URINARY CALCULOUS DISEASE

Edited by J. E. A. Wickham



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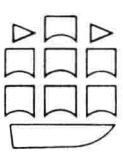
Edited by

J. E. A. Wickham

M.S., B.Sc., F.R.C.S.

Senior Consultant Urological Surgeon, St. Bartholomew's Hospital, London; Consultant Surgeon, St. Peter's Hospital Group, London; Sub-Dean, Institute of Urology, University of London, England; Consulting Urologist to the Royal Air Force.



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Urinary Calculous Disease

Preface

This book is an attempt to produce, in a reasonable compass, an up to date and logical account of the latest theories on the aetiology and treatment of urinary calculous disease.

Each section has been written by an acknowledged expert in his field and particular emphasis been laid on practicality, particularly in the areas relating to investigation and treatment. It has been a deliberate policy not to delve into biochemical detail in order to provide the practising clinician with a compact account of our current understanding of the stone problem.

Firstly, Professor W. H. Boyce and Dr. Martin Resnick present a historical perspective of the theories of renal calculus formation to the present day. Professor Norman Blacklock examines the effect of ethnic, environmental and dietary habits on the development of renal stones.

Professor Keith Anderson examines the anatomical basis for calculus formation in the kidney and Drs. Peacock and Robinson report on the nature of the various types of calculi encountered in man and consider the biochemical factors responsible for their development.

Mr. R. E. Williams describes the clinical presentation and investigation of the patient presenting with renal stone disease. Dr. Alan Rose reviews current concepts in the modern medical treatment of the patient with renal calculi and finally the Editor reviews current surgical practice for the operative cure of urinary stone disease.

The authors would like to thank Miss Freda Wadsworth of the Institute of Urology for her excellent line drawings and Mr. R. E. Bartholomew for the photographs. Miss G. H. Clark gave valuable assistance with proof reading and compilation of the index.

London, 1979 J.E.A.W

Contributors

C. K. ANDERSON, M.D., F.R.C.P.,
Professor of Pathology, University of Leeds at the General Infirmary, Leeds, England.

WILLIAM H. BOYCE, M.D.,
Professor of Urology, Department of Surgery, Bowman Gray School of Medicine, Winston Salem, North Carolina, U.S.A.

NORMAN J. BLACKLOCK, F.R.C.S.
Professor of Urology, University of Manchester; Formerly—Surgeon Captain R.N., Surgeon in Charge, Department of Urology, Haslar Royal Naval Hospital, Gosport, Hants, England.

MUNRO PEACOCK, F.R.C.P.,
Assistant Director, M.R.C. Mineral Metabolism Unit, The General Infirmary, Leeds, England; Honorary Consultant Physician, The General Infirmary, Leeds. Lecturer in Mineral Metabolism, University of Leeds, England.

MARTIN RESNICK, M.D.,
Urologist, Bowman Gray School of Medicine, Winston Salem, North Carolina, U.S.A.

WILLIAM G. ROBERTSON, B.Sc., Ph.D.,
Scientific Staff, M.R.C. Mineral Metabolism Unit, The General Infirmary, Leeds, England.

G. ALAN ROSE, D.M., F.R.I.C., F.R.C.P., M.R.C.Path.
Chemical Pathologist, St. Peter's Hospital Group and Senior Lecturer, Institute of Urology, University of London, England.

J. E. A. WICKHAM, M.S., B.Sc., F.R.C.S.,
Senior Consultant Urological Surgeon, St. Bartholomew's Hospital, London; Consultant Surgeon, St. Peter's Hospital Group, London; Sub-Dean, Institute of Urology, University of London, England; Consulting Urologist to the Royal Air Force.

R. E. WILLIAMS, M.S., F.R.C.S.,
Surgeon, Department of Urology, Leeds General Infirmary, Leeds, England.

Contents

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Aetiological theories of renal lithiasis: a historical review

Historical and archaeological studies clearly reveal that ancient man suffered from urinary tract stone disease. The earliest evidence dates to before 4 800 B.C. and was a bladder stone found among the pelvic bones of a young predynastic Egyptian. Another stone dating at about 4 200 B.C. was probably of renal origin and analysis revealed it to be composed of calcium carbonate, calcium phosphate and calcium oxalate (Shattock, 1905). Even in ancient times it was recognized that stone disease was not uniform throughout all populations in that urinary calculi were relatively common particularly in children in ancient Persia but were rare in Turkey (Desnos, 1914). Ancient records reveal that stone disease was also present in the Greek and Roman civilizations. Although the symptoms and treatment of the disorder were well recorded by ancient physicians it is surprising that early writers did not distinguish between renal and bladder calculi and wrote little regarding the causes of the disease.

Hippocrates can be credited with being the first to theorize about the aetiological factors of urinary lithiasis. He observed that many patients having calculi in the bladder or kidneys had sandy sediment in their urine and suggested that the ingestion of muddy river water or water containing lime caused stone formation in the urinary tract (Butt, 1956). Galen the great Roman physician also wrote about stone formation and recognized such risk factors as heredity, race, climate, diet, drinking water, the ingestion of alcohol, incidence of gout and rheumatism and metabolic abnormalities. Galen believed that gouty deposits and some renal calculi were of the same origin.

Ancient Indian physicians described four types of calculi which were formed by phlegm, vapour, bile and semen (Murphy, 1972).

> When air and phlegm meet, a small stone is formed which grows toward the bladder outlet and enters the outflow of urine. The tortured patient grinds his teeth, presses on his abdomen and rubs his penis. Urine flatus and faeces are passed with severe pain. In such a case, the stone is black, rough, irregular and covered with spikes like the maneleacadanba flower. The wise physician diagnosed the stone caused by air.

Most modern physicians would agree that this very accurately described the passage of a typical calcium oxalate stone. Bile stones were described as being small and smooth like an egg suggesting that they were in all probability uric acid calculi. Mediæval physicians attributed stone formation to a variety of causes: excess salt intake, excess heat, the presence in the urine of matter obstructing the kidneys.

With increased knowledge of the anatomy of the urinary tract and an under-

standing of renal physiology, modern physicians began to differentiate between kidney stones and bladder stones and this altered their concepts regarding those factors they believed to influence stone formation. This is clearly emphasized in the writing of Ron Delet (Murphy, 1972), a French physician practising in the 1500s:

> When waste is retained in the bladder, a stone will be produced, not in all, but in those who have a stricture of the meatus or suffer from retention of the urine. If these thick fractions fall down to the base of the bladder and remain there, they end in time by aggregating into stones. Stones differ in the two organs. Those found in the kidneys are formed by fine sands and assume the shape of the pelvis. Bladder calculi look like river pebbles, that is to say they are almost round and they are formed not with sand, but by an almost solid matter disposed in layers like an onion.

Jean-Baptiste van Helmont (1571–1644) was the first to suggest that stone formation resulted from the excretion of abnormal material in the urine (Butt, 1956). He observed that stone formation was associated with the presence of multiple factors and similarly the composition of the stone reflected the presence of multiple substances found in the urine. These necessary urinary factors were:

1. the spirit of urine (uric acid);
2. the coagulating spirit (alcohol);
3. a ferment causing decomposition of the urine.

He proposed the presence of a nucleus or core of the stone and progressive growth of the stone was dependent on the presence of a ferment causing decomposition of the urine.

The first investigations demonstrating the structural complexity of urinary calculi were made by Anton Von Heyden in 1684 (Butt, 1956). He removed the crystalline components from stones without destroying the gross structure and termed the remaining substance the 'framework' of urinary calculi. No attempt was made to identify the crystalline components themselves until 1776 when Carl Wilegim Schele a Swedish apothecary isolated uric acid from a calculus. French investigators Vauquelin and Fourcray and England's Wollaston and Marcet performed extensive chemical analyses and categorized stones as:

1. uric acid;
2. oxalate of lime;
3. cystine;
4. calcium carbonate;
5. phosphate of lime;
6. ammonium magnesium phosphates, and
7. fusible calculus consisting of the latter two substances.

In the 1800's many analytical investigations were carried out studying the composition and structure of calculi.

Alexander Marcet wrote in 1817 *An Essay in the Chemical History and Medical Management of Calculous Disorders*. He emphasized the importance of chemical analysis and discussed the importance of sawing through a calculus so that the internal structure can be studied. Marcet emphasized that stones formed in the kidneys and not the ureters and that the latter structure acted only as a conduit. Marcet was also one of the first of the modern investigators to discuss the relationship of diet and stone disease. He attributed the stone formation following

the French revolution to the improvement in the living conditions of the poor, but interestingly he also believed there existed other factors independent of diet and environment that increased an individual's propensity to form stones. He also recognized the prevalence of stones in certain regions and recorded the prevalence of the disease in districts and hospitals and determined the comparative frequency in different countries.

In the nineteenth century, scientists in different locations cooperated to a greater extent than previously which led to the furthering of concepts regarding stone formation and growth. Studies by William Bowman contributed much to the understanding of the process of urine formation by the kidney. In 1856 Meckel Von Hemsbach emphasized that stone formation is dependent on the encrustation of an organic substance by a precipitable material. He advanced the theory that the organic growing or cementing matrix was 'Meckel's stone forming catarrh' (Butt, 1956). Epstein in 1884 carried out analytical studies of stones and also concluded that urinary calculi contained a framework of albuminous substances. Like von Hemsbach he believed that inflammation of the urinary tract resulted in the sloughing of epithelial cells and subsequent formation of a ground work for the impregnation of inorganic urinary components. The work of Liesegang in 1896 demonstrated that if a gel of dilute potassium chromate is innoculated with a crystal the resulting precipitate forms in a discontinuous and periodic manner, a form which has subsequently been referred to as 'Liesegang rings'. The phenomenon was non-specific and it was originally theorized that the concentric laminations of stones represent 'Liesegang rings', however recent investigations tend to disprove this concept.

In the late 1800's with the development of cystoscopy by Nitze and diagnostic x-rays, new methods were employed to increase knowledge of aetiological factors in stone formation. Stones were recognized to occur with greater frequency in paraplegics and spinal patients and relationships between urinary stasis and infections with stone formation were better understood. Many investigations were carried out in the early twentieth century studying urostasis and stone formation. These showed that though stasis did not initiate stone formation, its presence potentiated urinary infection and the rate of stone growth.

Another interesting observation regarding the aetiology of stones was made by Osborne, Mendal and Ferry (1917) who observed that vitamin A deficient rats developed calcium carbonate and calcium phosphate renal stones. Subsequent studies by many investigators also equated stone formation and various dietary deficiencies. In his classic book *Stone and Calculus Disease of the Urinary Organs* Joly states:

> I believe the hypothesis that stone as a deficiency disease is the most plausable and probable that has been advanced. It explains not only the principle factors of the condition today, but also changes in its incidence in its past years. I believe that vitamin starvation acts primarily on the renal epithelium and through it on the colloid mechanism of the urine, also that once this mechanism is deranged, stone formation must follow as a direct result of a loss of physical chemistry.
>
> (Joly, 1929)

Other than dietary influences, Joly also recognized that geographic location, race, heredity, climate, chronic disease, congenital anomalies of urinary organs,

age and sex also influence stone formation. He was the first to emphasize the importance of a diathesis to stones and wrote:

> If stone is the result of a diathesis, it is only a symptom of a general disease, and a treatment should be directed mainly towards correcting the constitutional disturbance. If there is no diathesis the calculus itself becomes the paramount factor.

In 1923, Keyser reported the results of some extensive experimental studies of the effect of increased dietary calcium and oxalate administration of the production of crystallinuria and subsequent stone formation (Keyser, 1923). Based on these investigations, he proposed that hyperexcretion of crystals may cause stone formation and also recognized the protective effects of urine in maintaining crystalloids in solution. He believed that urine naturally contained a defence against extensive over concentration of normal urinary crystalloids and subsequent crystalline deposition and this mechanism was the first line of defence against stone production. This ability of urine was believed to be related to the hydrogen ion concentration and to the presence of protective colloids. Another factor of importance was the observation that when normal urine became super-saturated, the crystalline material is deposited in isolated, morphologically complete crystal units which have no tendency to fuse. Finally the last natural protection against stone formation lies in the anatomy of the urinary tract with its contractile and funnel shaped structures that allow for the ready passage of crystalline material. Keyser theorized that any disturbance in one or more of these protective mechanisms would result in stone formation.

With the use of new analytical and microscopic techniques made available by the advances of the twentieth century much knowledge has been gained in understanding the structural characteristics of calculi, the chemical composition, of its components and the various components present in the urine. Anatomical, metabolic and physical chemical studies have been carried out by numerous investigators, all trying to identify different factors that are associated with stone disease. Many theories have been proposed but none answer all of the questions. In all likelihood, an individual's stone diathesis will be found to result from the interaction of numerous factors, many of which have already been studied but surely others remain as yet unknown. In discussing the different theories about the modern concepts of stone formation, it is important to keep in mind the likely interaction and interdependence of these different factors.

Modern theories of stone formation and growth have concentrated on two separate but interrelated concepts:

1. the site of stone formation within the kidney; and
2. the physical mechanisms controlling stone formation and growth.

Obviously the stone must form somewhere, but whether it be in the renal tubule, collecting duct or pelvis remains controversial and several theories explaining the 'where' of stone formation have been proposed.

ANATOMICAL SITE OF STONE FORMATION

Randall's Plaques

In the late 1930's, Randall published a series of reports describing the presence of

papillary calcifications that he theorized were the precursor of primary renal calculus formation (Randall, 1937, 1940). Two types of lesions were recognized; the more common of which designated Randalls type I lesions measured 1–2 mm, were subepithelial and located not in the collecting ducts but in the interstitial tissue. Several plaques frequently involved one papilla and often more than one papilla in one kidney was involved in the process. These papillary lesions had three stages of development. In the first stage the plaques appeared microscopically as small cream coloured areas situated peripherally in the wall of the renal papilla which represented calcium deposition on the basement membrane of the collecting tubules. In the second stage the lesion presents itself as a small, irregular depression on the surface of the papilla and was termed the 'initial lesion'. At this stage the calcium deposition has spread intertubularly, causing shrinkage and stricture of the tubules which lose their epithelial covering and finally completely disappear. In the third and final stage a small dark deposit is seen on the calcium plaque which has lost its epithelial covering. This represents the beginning of a renal calculus. Careful and repeated microchemical analysis of these plaques reveals different ones to be composed of calcium phosphate, calcium oxalate and uric acid.

Randall believed that type I plaques gave rise to primary calculus formation. i.e. those calculi whose formation is unassociated with significant metabolic abnormalities. He postulated that since calculi are slow growing and typically located in a minor calyx these papillary deposits precede the development of the primary renal calculus.

The less common type II lesions consist of calcium salt deposition in the terminal portions of the collecting tubules and papillary ducts. This type is characterized by an inspissation of the terminal tubules of the papilla and each papillary tip is salt-encrusted. These are usually more frequently associated with urinary supersaturation and approximately half of the cases studied are associated with urinary infection. Type II lesions are characteristic of a hyperexcretory state and are seen in association with hyperparathyroidism, hypovitaminosis forms of renal infection and with nephrocalcinosis.

Randall studied a large number of kidneys removed at autopsy and found calcium salt deposition on one or more papilla in 19·6 per cent of the specimens examined. Other investigators working independently confirmed the presence of these plaques and also found them to be present in the same percentage of the population as Randall had noted (Rosenow, 1940; Posey, 1942). These and other studies revealed that the papillary lesions were twice as common in males than females and were more common in patients greater than 50 years of age. Vermooten (1942) studying a South African population found plaques to be present in 17·2 per cent of whites and only 4·3 per cent of Bantus; the latter group rarely formed stones.

Following this initial enthusiasm and confirmatory studies, followed reports and observations that contraindicated some of Randall's initial findings. Kjolhede and Lassen (1942) found calcium in kidneys free of papillary calcification and concluded that such calcific deposits were not a significant cause of renal stone formation and that other factors were of more importance. Other investigators demonstrated renal medullary, subepithelial calcium deposits in all kidneys examined and found no correlation between the degree of calcification and levels of

serum calcium, phosphorus, plasma urea nitrogen and urinary pH (Haggitt and Pitcock, 1971). Those with more advanced calcifications were associated with conditions predisposing to stone formation. These investigators surmised that possibly renal calcifications and subsequent stone formation was related to a lack of normal urinary inhibitors of crystallization. In a recent review, Prien (1975) emphasized that though most studies have confirmed the presence of Randall's plaques, their relationship to clinical stone disease is unknown. One of the major problems is that stone formation has its largest incidence in the third and fourth decade of life but Randall's plaques are found most frequently in subjects greater than 50 years of age. He correctly pointed out that without question factors other than papillary calcifications are of importance in initiating stone formation, however the true role of Randall's plaques has yet to be fully elucidated.

Carr's Theory

In 1953, Reginald Carr (1953) proposed an alternative hypothesis to explain the presence of renal stone formation in papillary regions. Like Randall he too noted that the process of stone growth probably depends on the presence of a nidus which is bathed in urine and fixed to the renal collecting system. Based on his own observations and those of others (Anderson, 1946), he suggested that the plaques that Randall observed were actually aggregations of microscopic calculi and not degenerative lesions of the papilla itself.

Carr studied a large number of kidneys or renal segments surgically removed because of the presence of stones and all specimens were studied microroentgenographically to detect the presence and location of microcalculi. After a radiopaque body was isolated, its components were determined by x-ray diffraction or powder radiography. Carr noted that practically all kidneys from patients greater than nine years of age contained microscopic opacities. He differentiated 'concretions' from 'microliths', microscopic calculi and true renal calculi, those bodies actually located in the calyces or pelvis. The microscopic concretions were found to lie just outside the fornices of the calyces in the corticomedullary zone or immediately beneath the renal capsule. He considered it most important that collections of these concretions occurred just outside the fornices of the calyces and were always in line with the arteries and veins. Concretions were often more numerous and larger in segments of the kidney that contained calyceal calculi. He noted that, frequently, small concretions would lie behind the base of a calyceal stone and behind these, more concretions of gradual diminution in size. In studies of multiple specimens Carr observed that the earliest detectable opacity is not of the papilla itself, but is in, or just outside of the extreme angle of the fornix. When these concretions were removed from the renal parenchyma they left a small endothelial lined cavity which did or did not communicate with the collecting system and in most instances the concretions were not adherent to the walls of the cavity.

Carr studied the renal lymphatics and observed that there existed three main plexuses:

1. subcapsular;
2. perinephric; and
3. plexus within the renal substance.

Carr theorized that since intrarenal concretions formed normally, there must exist a normal drainage mechanism for removing them. He believed this to be one of the purposes of the renal lymphatic system and suggested that renal calculi formed when normal drainage becomes impaired which could occur either because of overloading with an excessive number of microliths or by an impairment of drainage secondary to inflammation and fibrosis. This obstruction to drainage could be segmental or lobar and explains the process of stone formation within only one portion of the kidney. As expected, more microliths have been observed in the affected lobule than in other portions of the kidneys.

After concretions accummulate and grow, there occurs necrosis and subsequent breakdown of the membrane separating them from the renal tubules and urine. The presence of urinary salts in contact with the concretions permit growth and eventual true stone formation. With growth the calculus eventually extends into the cavity of the calyx and retention of the concretions at the papillary tip leads to aggregation, the formation of Randall's plaques, ulceration of the overlying mucosa and the subsequent deposition of urinary salts. X-ray diffraction studies of the concretions closely correlated with studies carried out by other investigators of true renal stones. Like Randall's theory, Carr's has yet to be completely reputed or confirmed.

Intranephronic Calculosis

The process of calculus formation within the nephron has been termed intranephronic calculosis. The entity was first described by Oliver and associates (Oliver, MacDowell, Whang, Welt, 1966) in the kidneys of magnesium depleted rats. Two types of deposits were recognized; one consisting of amorphous necrotic calcific cellular debris in the form of sloughed tissue within the tubules and the other consisting of structurally organized microcalculi lying in the lumen of the tubules especially in the thin loop of Henle. These had structural patterns which included layering of calcium and phosphorus upon a periodic acid shiff (PAS) positive mucopolysaccharide matrix. In his original description Oliver occasionally noted dilated tubules above an intranephronic microcalculus and he believed the process reproduced the pattern of stone formation. The process has been produced in the squirrel monkey (Drach and Boyce, 1972; Resnick, Oliver and Drach, 1978) and these studies similar to the theories of Randall and Carr suggest that intranephronic calculosis may actually represent the earliest form of stone formation.

Studies of renal biopsy tissue obtained from different types of stone formers and non-stone formers also provide some insight into the relationship of these intranephronic microliths and clinical stone disease (Malek and Boyce, 1973; Boyce, Willard and Prater, 1972). Fresh frozen specimens obtained from idiopathic calcium oxalate stone formers, all had intranephronic calculi present and the severity of the process directly related to the activity of the stone disease. Intranephronic calculosis was also present only in biopsies of non-stone forming patients undergoing prolonged milk-alkali therapy and in a patient with chronic pyelonephritis and colonic carcinoma. Interestingly no microliths were observed in kidneys of patients with magnesium ammonium phosphate, uric acid or cystine calculi.

Whether intranephronic calculi form within the lumen of the tubule or represent

material extruded from the tubule cells is unknown. Changes in mammalian tubular cells secondary to parathormone administration occur and are recognized as large granular accumulations of PAS positive mucopolysaccharides and electron dense bodies filling the cytoplasm (Engfeldt *et al.*, 1958). Structural alterations subsequently appear in the mitochondria and cellular destruction occurs. Possibly, Randall's plaques and Carr's intralymphatic calculi actually represent intranephronic calculi that have because of associated inflammation and obstruction migrated to a subepithelial or intralymphatic position.

The evidence certainly suggests that intranephronic calculosis has a role in calcium oxalate stone disease. Is this stone formation in its earliest stages or the result of stone formation from another process? The relationship between the severity of intranephronic calculi and the frequency of stone formation and their absence in renal biopsies from patients with struvite, uric acid or cystine calculi certainly suggests that they are a cause of and not the effect of calcium oxalate stone formation. As with the other theories of the 'where' of stone formation, further studies are required to either confirm or refute these observations.

BIOCHEMICAL CAUSES OF STONE FORMATION

Most theories concerned with the 'why' of stone formation conclude that crystallization and subsequent clinical stone formation occurs either because there exists in stone urine an excess of agents resulting in precipitation or stone urine lacks those agents which tend to inhibit crystallization. It should be emphasized that over the years a large amount of laboratory data has been accumulated regarding the crystallization of metastable solutions, the presence or absence of specific urinary proteins which are associated with stone formation and the importance of both organic and inorganic urinary inhibitors of crystal aggregation and growth, however many of the facets governing stone formation remain unknown. Though some of these facets will be discussed separately, it is likely that more than one is operational in either preventing or causing stone formation.

Precipitation-Crystallization

Probably no one area has been as extensively studied as that of the role of crystalloid saturation as it is related to urinary stone formation. Most students of stone disease would agree that in order for an individual to form a stone he must have urine super-saturated with regard to the specific ions comprising the stone (Pak, Diller, Smith and Howe, 1969; Robertson, Peacock, and Nordin, 1972). Urinary concretions without crystallization have not been recognized; even the radiolucent 'matrix' calculus contains crystals.

Prior to discussing the role of crystalloid supersaturation in urine as a cause of stone disease, it will be helpful to define several of the terms that apply to solubility theory. Urine may be undersaturated, supersaturated or oversaturated (Figure 1.1). *Saturation concentration* is that concentration of a solution at which the solid phase of the stone salt is in equilibrium with the liquid phase of the stone salt. Any solution with a concentration less than the saturation concentration is *undersaturated* and any with a concentration greater is *supersaturated*. Oversaturation is the supersaturation concentration at which spontaneous precipitation occurs. The

metastable region is that concentration between the saturation concentration and the oversaturation concentration.

Stone formation in saturated solutions involves three basic processes: crystal nucleation, crystal growth and crystal aggregation, and for purposes of review, it is convenient to discuss each separately.

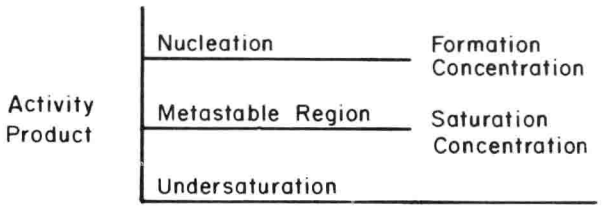

Fig. 1.1 Aetiological factors in renal lithiasis

Crystal Nucleation

Crystal nucleation is the establishment of the smallest unit lattice of a crystal species and can be either homogenous i.e. the nucleus is pure, or heterogenous i.e. a foreign body or other crystal form can lower the formation product with resultant crystallization. The crystal forms when a solution reaches a level of supersaturation such that an ion cluster particle becomes large enough for the surface energy and volume energy to be zero. At this point (formation product) the particle is at a critical size and will continue to grow as long as the solution remains supersaturated.

There is little reason to doubt that homogenous nucleation occurs in freshly voided urine. How frequently this occurs in the intact urinary passages and at what level is completely unknown. Finlayson (1977) utilizing the data known of renal tubular length and diameter, urine formation and flow rates and the theoretical rate of crystal formation and growth calculated that it would be very unlikely for free particles to grow at such a rate as to cause stone formation in the upper urinary tract. He believes that a particle must either be fixed to the wall of the renal tubule or nucleated on its surface before upper tract stone disease can develop. The turbulence, temperature change, alteration in pO_2, pCO_2 and ionic strength are other factors that may provide energy shifts capable of conversion of ion aggregates to crystal nuclei and subsequent growth to microscopic particles. More information is needed regarding changes in the concentration, electrical charges of the epithelium and other factors affecting the chemical thermodynamics of the collecting tubules and papillary surfaces before crystalluria in the test tube can be equated with crystalluria at the renal papilla.

Epitactic or heterogeneous nucleation occurs when non-crystalline molecules (usually large structures such as collagen or elastin) or another crystalline form serve to convert ion clusters from the solution to the nucleus or solid phase. Lonsdale (1968) first emphasized the similarities of the crystal surfaces of many common crystalline components of urinary calculi and suggested that the different components common to many calculi were secondary to epitaxial growth. Workers have since shown that calcium oxalate crystals can nucleate on uric acid (Meyer, Bergart and Smith, 1975). This mechanism is believed to account for the not

infrequent finding of hyperuricosuria in recurrent calcium oxalate stone formers (Coe and Kavalach, 1974; Smith, Hunt, King and Boyce, 1969). Studies by Pak (1971) suggest that a nidus of brushite may lead to the crystallization of calcium oxalate and others have suggested a protein-mineral interaction in initiating stone growth (Hench, 1972). Further studies are required before definite conclusion can be drawn regarding the importance of epitaxial growth and clinical stone formation.

Crystal Growth

The factors influencing crystal growth have been of great interest not only to investigators of stone disease but also to crystallographers and physical chemists. Crystal growth rates are a function of solution supersaturation with regard to the crystalloid ions. The greater the level of supersaturation, the greater the growth rate. Crystals cannot grow in undersaturated solutions, and if the conditions are proper, many will subsequently dissolve. Specific inhibitors of crystal growth are recognized (pyrophosphate, citrates), however the importance of these substances in inducing or preventing stone growth remains controversial. At this time concepts concerning crystal growth rates are of interest in a theoretical sense but as yet have not been found to be of value in either the evaluation of stone forming and potential stone forming patients or in appraising treatment programmes.

Crystal Aggregation

Since urinary calculi are polycrystalline, there is an obvious need for information relative to those mechanisms whereby crystal-crystal union transforms harmless crystalluria into an obstructive concretion. Crystalluria is not only more common in stone formers but the crystals also tend to be larger and more aggregated than in normal urine (Robertson, Peacock and Nordin, 1969; Robertson and Peacock, 1972). Smith (1976) studying ultrafiltrates of freshly voided urine demonstrated the presence of large aggregated crystals in the urine of 90 per cent of recurrent calcium stone formers, whereas less than one-fifth of normal subjects had similar findings. Interestingly after treatment, the frequency of crystalluria decreased to 46 per cent in this stone forming group. Possibly the aggregation of crystals is the initial phase of calcium oxalate stone formation and also possibly stone formers lack inhibitors of crystalloid aggregation rather than, as has been previously thought, of crystal nucleation.

Though crytalloid precipitation from a solution is dependent on the concentration of ions present (ionic strength) other important factors include temperature and pH. Extensive studies carried out at the Mineral Metabolism Unit in Leeds (Nordin, 1973) have demonstrated that calcium oxalate and calcium phosphate crystallization occurs at essentially the same ionic strength in both normal and stone forming urine as in simple buffers. Though stone-formers tend to excrete more calcium in their urine than non-stone formers, there exist many individuals with elevated urinary calcium levels who have never formed a stone, and conversely, many stone-formers who are normocalciuric.

Stone-formers excrete more saturated urine with calcium salts than non-stone-formers, but not to a degree to cause spontaneous crystalluria (Robertson, Peacock and Nordin, 1968). It is of interest that though increased calcium oxalate