Urinary Calculi: Review of Classification Methods and Correlations with Etiology

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URINARY CALCULI: REVIEW OF
CLASSIFICATION METHODS AND CORRELATIONS WITH ETIOLOGY

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Abstract

Current physical and chemical methods available for urinary stones analysis are critically reviewed. No one method is sufficient to provide all the clinically useful information on the structure and composition of the stones. We show that a combination of refined morphological and structural examination of stone with optical microscopy, complemented by compositional analysis using infrared spectroscopy of the core, cross-section and surface of calculi, provides a precise and reliable method for identifying the structure and crystalline composition, and permits quantification of stone components while being highly cost effective. Using such morphoconstitutional studies leads to a classification of urinary stones in seven distinctive types and twenty-one subtypes among monohydrate (whewellite) and dihydrate (weddellite) calcium oxalates, phosphates, uric acid, urates, protein, and cystine calculi. Furthermore, all of the recognized sub-types exhibit correlations with specific pathophysiologic conditions. We conclude that such morphoconstitutional refined analysis and classification of urinary calculi is of interest to properly identify the type of stone disease and provides clues to etiopathogeny.

Key Words: Urinary calculi, stone analysis, morphoconstitutional classification, calcium oxalate, calcium phosphate, urates, cystine, protein stones, etiopathogenic factors.

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Introduction

Recent worldwide and nation-wide epidemiologic data provide evidence that incidence of renal stone disease has strikingly grown in industrialized countries from World War II in parallel with increasing affluence and correlative changes in nutritional habits (3, 80, 114, 115). In addition, comparative studies on stone composition in Western countries over the past four decades have shown a dramatic increase in the proportion of calcium oxalate (CaOx) as the main component, contrasting with a stable incidence of cystine and uric acid stones and a marked decrease in the incidence of infection stones (83, 129).

In view of the present high incidence of nephrolithiasis, a renewed interest is directed to pathophysiology of stone formation, especially with concern to calcium oxalate and/or phosphate stones. In this respect, careful morphological and structural analysis of calculi, either spontaneously passed or surgically removed, provides information of major interest on the physico-chemical conditions which cause the formation and growth of stones in a given patient.

Present classifications of urinary stones are mainly based on chemical composition and epidemiological considerations. In the present paper, after having discussed the main characteristics of stone analysis methods and the results of current stone classifications, we attempt to show that using a combination of light microscopic examination and infrared (IR) spectroscopy analysis provides a simple and useful means to classify urinary stones (Table 1). Furthermore, clinical and biochemical data associated with each stone type and subtype strongly suggest that in most cases, stone typology can be a useful indicator of stone etiopathogeny (Tables 2-4).

Methods of Urinary Calculi Analysis

Introductory remarks

Urinary calculi result from a transient, intermittent or permanent disorder in urine composition that induces urine supersaturation. The first step in calculus formation is nucleation, followed by growth around the initial

Table 1. Morphoconstitutional classification of urinary calculi.

Type	Surface	Section
Ia	Smooth, mammillary or mulberry-shaped. Frequent single umbilication indicative of papillary origin. Color: brown (Fig 1).	Compact. Concentric structure, radial crystallization. Brown (Fig 1).
Ib	Both mammillary and rough. Some mamillae broken or hollow; no umbilication. Color: dark brown (Fig 2).	Compact with some gaps. Crystalline without organized structure. Dark brown (Fig 2).
Ic	Smooth or budding. Cream to light brown (Fig 3).	Compact, crystalline, finely granular without organized structure. Light color (Fig 3).
Id	Smooth Color: pale brown (Fig 4).	Compact, microcrystalline structure; thin concentric layers. Color: beige (Fig 4).
IIa	Spiculated, with aggregated bipyramidal crystals. Bright, translucent with sharp angles and edges. Color: pale yellowish-brown (Fig 5).	Crystalline Diffuse loose radial crystallization. Yellowish-brown (Fig 5).
IIb	Spiculated, with thick, entangled, dull, opaque bipyramidal crystals, having blunt angles and edges. Cream to pale yellowish-brown (Fig 6).	Compact, crystalline, without organized structure. Gray-beige to yellow-brown. (Fig 6).
IIc	Rough, microcrystalline. Gray-beige to dark yellow-brown (Fig 7).	Microcrystalline with peripheral diffuse concentric structure. Core with loose unorganized structure. Gray-beige to dark yellow-brown (Fig 7).
IIIa	Homogeneous, crystalline, smooth or slightly embossed. Various colors: ocher, orange, yellowish or gray-beige (Fig 8).	Compact concentric structure, Radial crystallization. Ocher to red-orange (Fig 8).
IIIb	Heterogeneous, locally crystalline or microcrystalline, rough or porous. Various and heterogeneous colors whitish to brownish-red (Fig 9).	Compact or loosely crystalline, unorganized structure. Frequent porous areas. Orange to red-orange (Fig 9).
IIIc	Homogeneous, rough, locally porous. Microcrystalline. Color: whitish to gray-brown (Fig 10).	Compact, microcrystalline. Usually unorganized or with weakly apparent concentricity. Gray to gray-brown (Fig 10).
IIId	Heterogeneous, microcrystalline, rough and extensively porous. Color: grayish to brown (Fig 11).	Heterogeneous, with loose concentric layers, locally porous. Gray-beige to brown (Fig 11).
IVa1	Homogeneous, microcrystalline, rough, finely embossed. Color: whitish to beige (Fig 12).	Homogeneous, microcrystalline, crumbly with or without concentric structure. Whitish to beige (Fig 12).
IVa2	Homogeneous, crystalline, smooth with glazed appearance and cracks. Irregular shape with asperities like silex splinters. Color: brown-yellow (Fig 13).	Heterogeneous concentric foliated structure. Thick crystalline brown-yellow layers and thin microcrystalline beige layers. Often multiple concentricity surrounding distinct nuclei (Fig 13).

Table 1. Morphoconstitutional classification of urinary calculi (**continued from previous page**).

Type	Surface	Section
IVb	Heterogeneous, both rough and embossed, sometimes porous, with confluent superficial deposits. Color: whitish or beige, brown-yellow to brown (Fig 14).	Heterogeneous, concentric structure with alternately thick whitish, microcrystalline layers and thin, brown-yellow crystalline layers (Fig 14).
IVc	Homogeneous, crystalline, composed of amalgamate crystals with blunt angles and edges. Color: white (Fig 15).	Loose structure with crude radial crystallization and sometimes diffuse concentric organization. Frequent presence of other compounds which slightly modify morphology. Whitish (Fig 15).
IVd	Homogeneous, crystalline, finely rough or dappled. Frequent slightly translucent aspect. Color: whitish to beige (Fig 16).	Compact concentric layers with radial crystallization. Whitish to beige (Fig 16).
Va	Homogeneous, crystalline, either granular with blunted-angle crystals or only embossed. Translucent, waxy aspect. Color: yellowish to brown-yellow (Fig 17).	Homogeneous. Unorganized or with crude and diffuse radial crystallization. Yellowish to pale brown-yellow (Fig 17).
Vb	Homogeneous, microcrystalline, smooth or very finely rough. Color: whitish to yellowish (Fig 18).	Heterogeneous, compact with microcrystalline whitish thin concentric layers in periphery. Crystalline, unorganized core. Yellowish to pale brown-yellow (Fig 18).
VIa	Soft calculi. Homogeneous, smooth, without organized structure. Often translucent aspect. Color: whitish to pale brown (Fig 19).	Homogeneous, unorganized (same aspect as the surface). Foci of secondary mineralization often present. Whitish to pale brown (Fig 19).
VIb	Heterogeneous, irregularly rough, locally scaled. Color: brown to blackish (Fig 20).	Heterogeneous, slightly organized. Crumbly, with crude and diffuse concentric and foliated structure. Dark brown blended with color(s) of associated components (Fig 20).
VIc	Homogeneous, smooth or finely rough, with clefts and scales. Color: brown to blackish (Fig 21).	Homogeneous, unorganized, loose, dark-brown or heterogeneous, with a brown proteic shield surrounding a loose, unorganized core made of light-brown whewellite crystals (Fig 21).
VII	Miscellaneous	See text for comments

nucleus. Factors acting on stone growth may be different from those involved in nucleation (30, 44, 134). Also, physico-chemical conditions that had provoked stone nucleation may have disappeared at the time of patient's investigation. In both cases, separate examination of the core, cross-section, and surface of the calculus, may provide information as regard the lithogenetic conditions that were present at the time of nucleation and during subsequent stone growth. Such information is of primary importance in the reconstruction of the history of calculus formation.

Some remarks on general characteristics of urinary stones may help to select the best combination of analytical methods. Stone components may be mineral, organic, or both. More than 65 different molecules (including 25 of exogenous origin) have been found in urinary calculi (29). The same chemical component may crystallize in different forms [for instance, calcium oxalate may be present in the form of CaOx monohydrate (COM), or dihydrate (COD), or trihydrate (COT), and such crystalline forms have been shown to be associated with distinct biochemical conditions (2, 31, 37). Therefore, proper stone analysis has to identify not only the molecular species present in the calculus, but also the crystalline forms within chemical constituents.

Most stones are of mixed composition and, among heterogeneous calculi, about 80 % are made of a mixture of CaOx and calcium phosphate (CaP) in various proportions. By contrast, the presence of a unique, but unusual compound (e.g., 2,8-dihydroxyadenine, xanthine,

cystine, calcite, etc.) defines a specific type of urolithiasis.

Quantitative evaluation of components is needed to provide full information. Location of components within the calculus has to be considered. A small quantity of CaOx concentrated in the core of a phosphatic stone is suggestive of a changing lithogenetic process initiated by calcium oxalate supersaturation and subsequent modification by factors which increase urinary pH, such as urinary tract infection, whereas a small quantity of CaOx located in peripheral layers has no etiopathogenic significance (65). The same is true for CaP. When present in small quantity in the nucleus of a calculus predominantly made of CaOx, CaP is often suggestive of stone formation through heterogeneous nucleation, for instance on a Randall's plaque (108, 109).

Superficial and cross-sectional morphology of stones depends not only on molecular composition and on crystalline form, but also on anatomic conditions (such as pyelocaliceal dilatation and stasis or tubular ectasias as in medullary sponge kidneys) and metabolic activity of stone disease. Color, texture, structural features, such as papillary umbilication, bracketing sides, shape and size of the crystals, are significant features which give information on the age of the stone, possible processes of crystalline conversion, and presence of other small calculi *in situ*.

Microscopic examination may provide information on stone activity and lithogenetic process. For instance, a dark-coloured whewellite stone can be usually considered an old inactive calculus with a slow growth rate which has allowed the incorporation of high quantities of urinary pigments in the inner and superficial layers. By contrast, a very pale coloured whewellite structure is the evidence for fast crystalline growth and very active lithogenetic process such as observed in primary hyperoxaluria or in enteric hyperoxaluria (51). These features have to be taken into account for stone classification as developed in detail below.

Analytical methods

Stone analysis is based on chemical and physical methods (46, 85). It may be emphasized that no single method provides total information about the structure and composition of stones. Preferably, at least two different methods (including one physical technique) have to be combined for accurate analysis of calculi. A critical review of the methods has been published (39). We will briefly address the possibilities and limitations of the main available analytical methods.

Chemical methods do not give information about crystalline phases and do not detect rare drug-induced or metabolic compounds, such as 2,8-dihydroxyadenine (18), xanthine, triamterene, or silica. Moreover, these

Figure 1. Type Ia stone. **1a.** Stone with smooth and mammillary surface. Note the presence of a papillary umbilication. Color: brown to dark brown. Composition: whewellite. Dimensions: 5 x 3.5 x 3 mm. **1b.** Section composed of concentric layers with radial crystallization. Color: dark brown. Composition: pure whewellite. Dimensions: 6 x 5 x 5 mm.

Figure 2. Type Ib calculus. **2a.** Rough and mammillary surface. Color: yellowish-brown to dark brown. Composition: whewellite (93%) + proteins (5%) + carbapatite (2%). Dimensions: 12 x 9 x 7 mm. **2b.** Unorganized cross-section. Note the presence of some gaps. Color: dark brown. Composition: whewellite (94%) + proteins (5%) + carbapatite (1%). Dimensions: 11 x 7 x 5 mm.

Figure 3. Type Ic calculus. Composition: pure whewellite. **3a.** Smooth and budding surface. Note the very light color: beige to pale yellowish-brown. Dimensions: 12 x 7 x 5 mm. **3b.** Finely granular and unorganized core. Note only some concentric layers with radial structure in peripheral areas. Color: cream to yellowish-brown. Dimensions: 10 x 8 x 6 mm.

Figure 4. Type Id calculus. Composition: pure whewellite. **4a.** Smooth surface. Color: pale brown. Dimensions: 3 x 3 x 2 to 8 x 6 x 5 mm. **4b.** Section mainly composed of thin concentric layers. Note the radial striations of peripheral layers that correspond to some areas with type Ia structure. Color: beige. Dimensions: 16 x 10 x 8 mm.

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techniques frequently give false-positive or false-negative results (28, 84) and cannot guarantee a correct quantitation of the molecules except for procedures based in fact on physical methods able to simultaneously detect and quantify ions, such as atomic absorption spectrometry for calcium and magnesium (61), or ultra-violet (UV) spectrometry for urate, phosphate (73, 132), or drugs (113).

A number of physical methods for stone analysis are available (39, 116). While specific methods can be used for the characterization of unusual compounds (19), or to evaluate peculiar aspects of the stones [e.g., the study of trace elements content (69, 78, 135)], routine analysis must be able to give comprehensive information on stone composition for clinical purposes. The following two analytical approaches are useful and complementary:

1. Microscopic examination with either a dissecting (38, 107, 112), or polarizing (8, 14, 20, 90, 117, 122, 123), or scanning electron microscope (11, 21, 70, 71, 86, 91, 125). Such methods provide information about the nature of crystalline components, shape of the
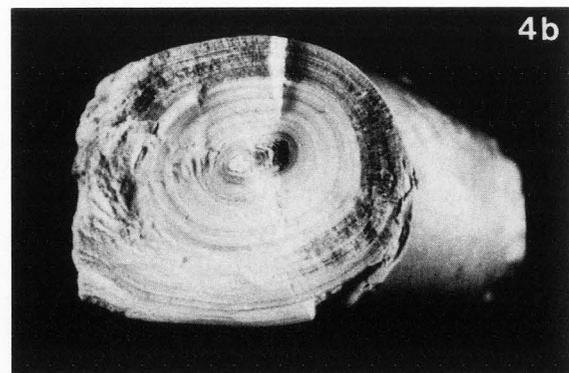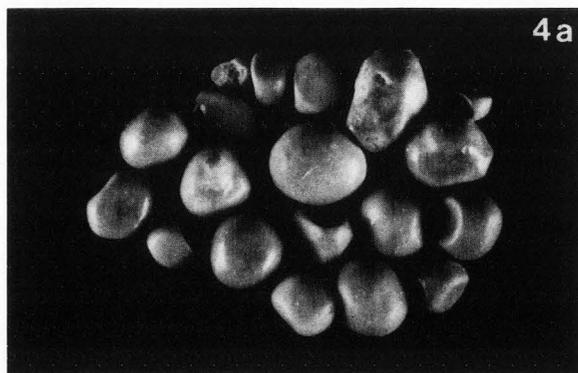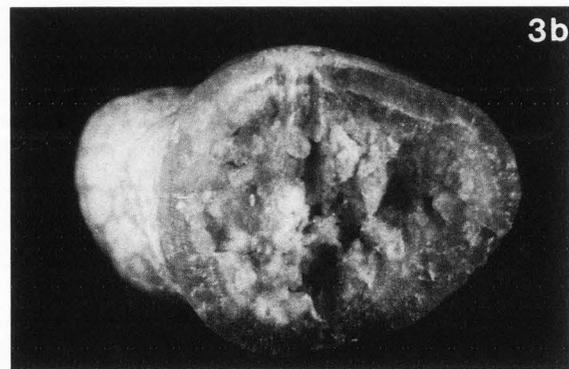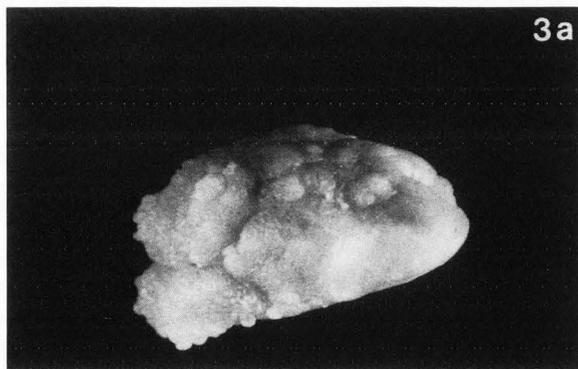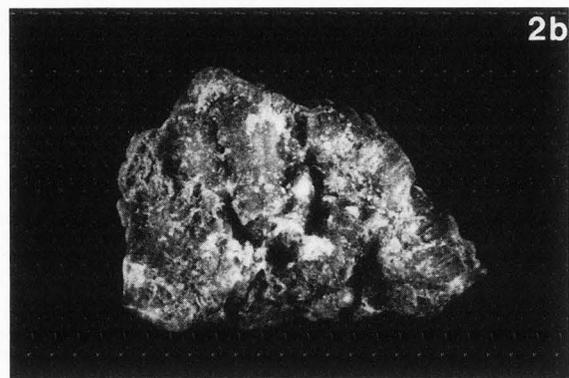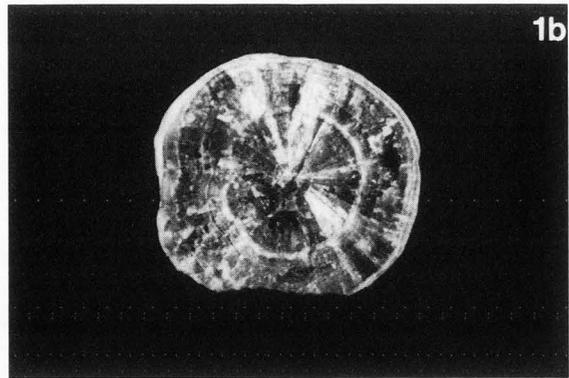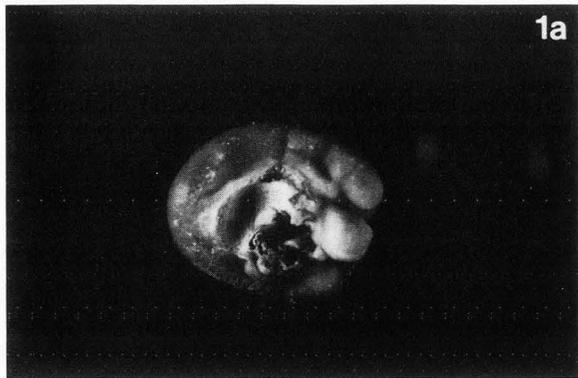
crystals, internal structure, location of components, crystalline conversions (20, 122, 123), and some data about intimate relations between crystals and organic matrix (12, 13, 45, 141) or epitaxial relationships between different crystalline species (87). Transmission (TEM) and scanning electron microscopy (SEM) have been largely applied to study the inner structure of calculi (23, 110, 137) and to demonstrate the morphology of small crystals (11, 21, 125). For instance, using these methods, frequent nucleation of calcium oxalate stones on apatite nucleus was emphasized (1, 20, 107), and studies of the papillary calculi were performed (21).

2. Identification of components in the stone is the second step. Crystallographic methods (43, 49, 55, 101, 105, 118, 127), thermal analysis (7, 77, 111, 126), and IR (5, 6, 35, 58, 95, 131, 138) or Raman spectroscopy (36, 92), are available for this purpose.

Among these, X-ray diffraction (XRD) and IR spectrometry are the most convenient ones. Initiated by Saupe in 1931 (118), XRD methods have been extensively used to analyze stones (4, 55, 57, 82, 99, 120, 121, 136), but they cannot detect all the components present as has been shown by several comparative studies (14, 29, 77, 127). First applied to stone analysis by Beischer (5) and by Weissmann et al. (138), IR spectroscopy spread mainly in Europe where numerous studies were performed using this technique (6, 28, 35, 58, 95, 121, 130). The quantity of sample needed for Fourier-Transform IR (FTIR) spectrometry can be less than one microgram; using IR microscopy (33), a single 10-20 μm crystal can be studied. As for XRD, computerized data can be automatically interpreted (9, 60, 74). Procedures and atlas of various spectra have been published (59, 97) and quantitative analysis is possible (59, 79). Infrared analysis is an easy and rapid procedure, able to identify all crystalline and amorphous compounds. Thus, IR spectroscopy can be considered a valuable technique for stone analysis as confirmed by international quality controls on urolith analysis (111, 133).

Review of Stone Classifications

Classifications based on stone composition

Epidemiologic data on stone composition contribute to the knowledge of the main causes of urolithiasis disease in a country during a given period (3). Four groups of stones, grossly related to different etiopathogenic factors, are usually distinguished: calcium stones, uric acid stones, infection stones, and cystine stones.

Such a classification is useful to roughly compare the risk factors in a defined population. For instance, it can be shown that the sex ratio (males/females, M/F) is higher in calcium and uric acid stones than in infection stones (99, 140), indicating that females are more frequently exposed to the risk of infection stone and males to metabolic disorders (102).

From an epidemiologic point of view, some authors report the overall frequency of the components while others describe their results as main components (i.e., substances which account for more than 50% of the stone). Data on mixed calculi often are missing or reported as of little concern (44, 105).

In 1962, Herring (55) analyzed the first large group of stones by XRD and found whewellite in 43% and weddellite in 61% of the stones. This was surprisingly the only report to mention weddellite as the most frequent CaOx form in urinary calculi. In 1963, using XRD and polarizing microscopy, Prien (106) reported that CaOx was present in about 67% of 24,000 stones. More recently, similar results were obtained by Mandel and Mandel (83) in the U.S.A. and by Schmucki and Asper in Switzerland (120), with CaOx in 68.4% and 76% of 3833 and 14165 calculi, respectively. In agreement with the findings of Brien et al. (14), we found that 82.7% of 4600 calculi analyzed by IR spectroscopy contained CaOx, mainly as whewellite (82%). Recently, Leusmann (77) published the composition of 5035 calculi examined by XRD and found whewellite in 70.3% and weddellite in 43.6% of the samples. Results concerning weddellite are similar to those reported by Prien (106), Schmucki and Asper (120), and Mandel and Mandel (83), but higher frequencies were noted in our experience (56.8%) and in the studies reported by Brien et al. (59.1%) or Herring (61%) (14, 55).

In view of the large group of stones analyzed, the observed differences probably are due to analytical problems rather than true differences in stone composition. Such difficulties are clearly apparent for apatite, the frequency of which varies from 27.8% for Brien et al. (14) up to 61.5% for Herring (55) although both authors use the same analytical method (XRD), whereas we were able to detect apatite in 75.6% in a group of 4600 calculi studied by IR spectroscopy (29). From an epidemiological point of view, such discrepancies are truly of minor importance, since only the main compounds must be considered. However, for a particular patient, it may be very important to identify small quantities of apatite or other components located in the nucleus of the stone or in a given area, because such information can point to a specific process of stone nucleation or growth. Separate analyses of nucleus and peripheral layers should be performed on all calculi (4, 39).

Calcium stones

A number of physicians consider "calcium stones" as a unique class of stones, although this class actually
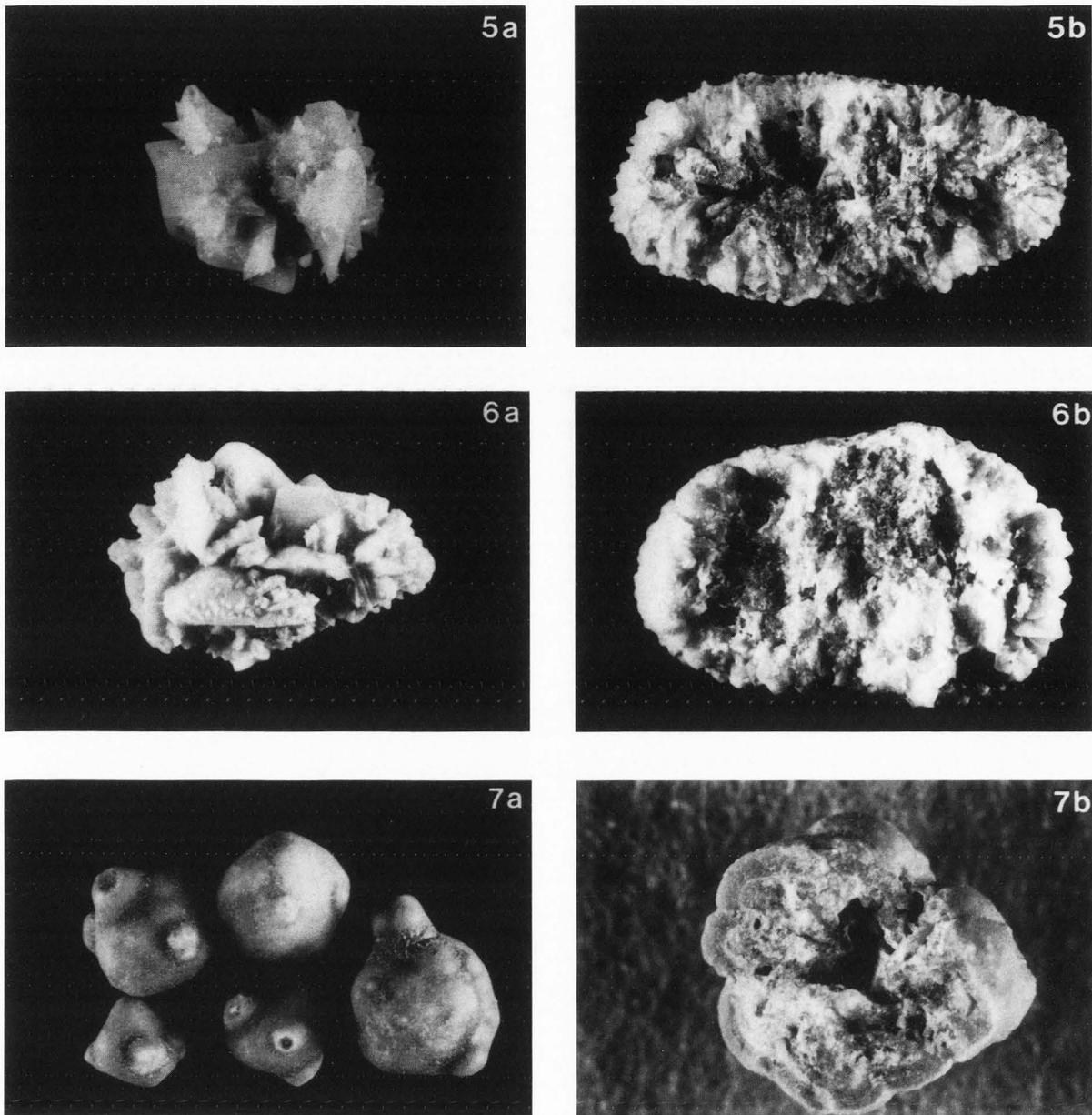
Figure 5. Type IIa stone. Composition: weddellite (95%) + carbapatite (3%) + whewellite (2%). Color: pale yellow-brown. **5a.** Spiculated surface. Dimensions: 5 x 3.5 x 3 mm. **5b.** Cross-section made of diffuse loose radial crystallization. Dimensions: 15 x 15 x 6.5 mm.

Figure 6. Type IIb stone. **6a.** Spiculated surface, with thick, entangled and opaque bipyramidal crystals. Color: beige. Composition: weddellite (65%) + whewellite (35%). Dimensions: 6 x 4 x 3.5 mm. **6b.** Compact unorganized cross-section. Color: yellowish-brown. Composition: whewellite (60%) + weddellite (35%) + carbapatite (5%). Dimensions: 15 x 9 x 6 mm.

Figure 7. Type IIc stone. **7a.** Rough and embossed microcrystalline surface made of very small bipyramidal crystals. Color: yellow-brown. Composition: weddellite (85%) + whewellite (10%) + proteins (4%) + carbapatite (1%). Dimensions: 5 x 4 x 4 to 8 x 6 x 5 mm. **7b.** Typical cross-section with loose core and thin concentric peripheral layers. Color: gray-beige. Composition: weddellite (90%) + whewellite (7%) + proteins (3%). Dimensions: 5 x 5 x 4 mm.

includes various molecular compounds (CaOx, CaP, magnesium and calcium phosphate). Moreover, these components may be present in different crystalline phases both for CaOx [whewellite, weddellite, and, rarely (42), calcium oxalate trihydrate], and CaP (carbapatites, amorphous CaP, octacalcium phosphate, brushite).

The clinical relevance of distinguishing crystalline phases is rarely considered. However, some studies on relationships between composition and cause of the calculi have suggested that weddellite or weddellite-like structures are more frequent in the stones produced by patients with hypercalciuria (37, 88). Furthermore, weddellite is spontaneously formed in solutions with high calcium/oxalate molar ratio (15, 31, 40, 41). Meanwhile, whewellite is observed for low calcium/oxalate molar ratio and in hyperoxaluric conditions (41). Recently, Conte *et al.* (27) compared stone composition determined by IR spectroscopy with biological data in 58 subjects: 28 had formed a stone mainly composed of whewellite and were normocalciuric; in contrast, the other 30 patients had stones either composed of mixtures of CaOx (without further precision on the crystalline phase) and CaP, or made up of weddellite, and were hypercalciuric. These authors concluded that weddellite stones were more frequent in hypercalciuric patients (27). They also suggested that whewellite stones probably are related to a lack of inhibitory activity, but they did not provide conclusive arguments about such defect (27).

On the other hand, it is largely accepted that urine contains several crystallization inhibitors. Among them, citrate (67, 103) and macromolecular substances such as nephrocalcin and Tamm-Horsfall protein (56, 89) have been reported to possess a strong inhibitory activity against the growth or aggregation of CaOx monohydrate.

Concerning the interest to distinguish between pure CaOx stones, CaOx and CaP mixed stones, and pure CaP stones, it can be first argued that, contrary to CaOx, crystallization of CaP is strongly dependent on the urinary pH. Thus, stones predominantly composed of CaP develop in alkaline or weakly acidic urine. Such pH-dependency is not found in common idiopathic CaOx nephrolithiasis. Several workers have emphasized the relationship between CaP stones and disorders in renal acidification (47, 48, 72). In their studies, Gault *et al.* (47) reported a predominant CaP (without struvite) composition in 11.5% of 4014 calculi studied by means of IR spectroscopy. The sex ratio (M/F) was close to 1, whereas in patients with CaOx-rich stones the M/F ratio was above 3. A selected group of 23 patients producing CaP stones was compared to another group of 29 CaOx stone formers. Metabolic investigation, including acidification tests, were performed on the two groups. A third of the patients in the CaP group had evidence of

incomplete renal tubular acidosis versus none in the CaOx group (48). Recently, Ohman *et al.* (96) compared the clinical significance of phosphate in 52 CaOx stone formers. They conclude that "pure calcium oxalate stones may be the result of high oxalate excretion whereas other calcium containing stones may have another and probably more complex aetiology".

In view of these data, and additionally considering that CaP stones are frequently larger and more recurrent than CaOx stones, it can be concluded that it is of clinical interest to classify CaOx stones and CaP stones into two separate groups. The main problem encountered here is to define the demarcation line between the groups because a great number of calcium stones are mixtures of CaOx and CaP in various proportions. In their study, Gault *et al.* (47) included in the oxalate group stones which contained 90% or more of CaOx and in the phosphate group stones with a CaOx/CaP ratio of less than 1. In fact, the limit of 50% to include patients in the phosphate group is criticizable because frequently in a given patient, who produced several mixed calcium stones, some stones contain more than 50% CaP, whereas others contain more than 50% CaOx. Probably, it would be better to adopt the limit above 65-70% to define phosphate and oxalate stones and to include the intermediate stones in a class of CaOx and CaP mixed stones.

Infection stones

Usually, this group defines stones which contain struvite and result from chronic urinary tract infection (UTI) by urea-splitting organisms such as proteus, staphylococcus epidermidis, ureaplasma urealyticum and others (52, 75). The responsibility of UTI by non-urease producing bacteria in the genesis of another calculi, especially CaP stones without struvite, is poorly documented. Some investigators have demonstrated the ability of bacteria such as *Escherichia coli* to induce precipitation of CaP (26, 54, 68). Holmgren *et al.* (62) reported a prevalence of UTI close to 50% when calculi were predominantly made of CaP without struvite. By contrast, UTI was significantly less frequent in CaOx stone patients (26%).

We observed similar findings in a group of 2094 patients. Among them, 630 (30%) had UTI. Calcium oxalate was the main component of 1333 stones and only 17.1% of the corresponding patients had UTI. When calculi were predominantly made of carbapatite without struvite, UTI was present in 46% of the cases. These results suggest that UTI by non-urealytic bacteria may be a significant and particular cause of CaP stone formation. As early as 1947, Prien and Frondel (105) concluded that pure apatite stones belong to the infection stones group even if the urine may be temporary acidic

Table 2. Surface morphology of calculi and corresponding pathophysiologic factors.

Type	Usual Composition	Main Etiologic Conditions
Ia	Whewellite	Intermittent hyperoxaluria (with or without hyperuricosuria). Medullary sponge kidney; Randall's plaque (umbilication).
Ib	Whewellite	Hyperoxaluria; stasis.
Ic	Whewellite	Primary hyperoxaluria.
Id	Whewellite	Hyperoxaluria (multiple, confined stones).
IIa	Weddellite	Hypercalciuria
IIb	Weddellite + whewellite	Hypercalciuria + intermittent hyperoxaluria.
IIc	Weddellite	Hypercalciuria (multiple, confined stones).
IIIa	Anhydrous uric acid	Low urinary pH, stasis
IIIb	Dihydrate uric acid and/or anhydrous uric acid	Hyperuricosuria; low urinary pH; Defective renal ammoniagenesis; ileostomy.
IIIc	Various urates	Hyperuricosuria + high urinary pH.
	Al-Mg urate	High urate concentration + aluminum-containing phosphate binders (end-stage renal failure).
	Ammonium hydrogen urate	Malnutrition (low phosphate intake); hyperuricosuria + high urinary pH and ammonium.
IIId	Ammonium hydrogen urate	Infection with ammonia-producing organisms; laxative abuse; High renal ammoniagenesis.
IVa1	Carbapatite ± oxalates	Urinary tract infection; hypercalciuria; defective renal acidification.
	Carbapatite + struvite	Infection with urease-producing organisms.
IVa2	Carbapatite	Primary or secondary renal tubular acidosis (complete or incomplete).
IVb	Carbapatite + struvite	Infection with urease-producing organisms.
	Carbapatite ± oxalates	Primary hyperparathyroidism.
IVc	Struvite	Infection with urease-producing organisms.
IVd	Brushite	Primary hyperparathyroidism; hypercalciuria; Renal phosphate leak.
Va	Cystine	Cystinuria
Vb	Cystine + small amounts of carbapatite	Cystinuria + alkali therapy.
VIa	Proteins	Urinary tract infection.
VIb	Proteins + other components	Proteinuria + metabolic and/or drug-induced components.
	Proteins + carbapatite ± struvite	Urinary tract infection.
VIc	Proteins + whewellite	End-stage chronic renal failure; chronic hemodialysis.

Table 3. Most frequent mixed surface morphology of calculi and corresponding pathophysiologic factors.

Type	Usual Composition	Main Etiologic Conditions
Ia + IIa	Whewellite + weddellite	Intermittent hyperoxaluria and hypercalciuria.
Ia + IIa + IVa	Whewellite + weddellite + carbapatite	Intermittent hyperoxaluria + hypercalciuria. Medullary sponge kidney + hypercalciuria.
IIa + IVa	Weddellite + carbapatite	Hypercalciuria; primary hyperparathyroidism.
Ia + IIIb	Whewellite + uric acid	Hyperuricosuria + intermittent hyperoxaluria.
Ia + IVa	Whewellite + carbapatite	Medullary sponge kidney; intermittent hyperoxaluria + infection with non urease-producing organisms.
IVa + IVc	Carbapatite + struvite	Infection with urease-producing organisms.

and germ-free. Obviously, relationships between CaP stones and bacteria need further investigation.

The possibility that infection may induce CaP stones is an additional argument to separate calcium stones into distinctive groups.

Morphoconstitutional classifications

The superficial and inner appearance of the stone is well known since the 18th century and only few details of structural interest were described later using new microscopic techniques, mainly but not only SEM (8, 17, 81, 94, 119). First attempt to morphoconstitutional classification was made by Ord and Shattock (98) about the calcium stones. They defined five types in relation to the structure of the calculus: concentric layers (type I), concentric layers with radial laminations (type II), shape and structure analogous to Jackstones (type III) (107), loose unorganized structure (type IV), and compact unorganized structure (type V).

Prien and Frondel (105) confirmed such morphologic types, but they did not continue on the morphological classification because they were convinced that virtually all the stones, except cystine and other rare compounds, could be clinically grouped into three classes as proposed by Jensen in 1941 (64): class I, for CaOx and mixtures of CaOx and CaP; class II, for struvite-containing stones; and class III for uric acid stones.

In 1962, Murphy and Pyrah (88) distinguished mainly between three types of structures consisting of: laminated type, with concentric layers often presenting alternate structure (e.g., mixed stones composed of carbapatite and struvite or of carbapatite and weddellite); crystalline type in which the crystals appear well-formed and individualized (this type essentially corresponds to weddellite or whewellite); and striated type, in which the crystals are frequently oriented resulting in an appearance of radial striation. This type was observed in whewellite stones, as well as in uric acid and brushite stones (16, 128). The crystalline and striated types mainly concerned stones composed of CaOx.

More recently, Schubert and Brien (122) investigated the relationships between the textural forms of CaOx stones and their composition; they identified four textural types and concluded that whewellite can form either by primary crystallization or by dehydration of weddellite and conversion to whewellite. Similar conclusions were drawn by Berg *et al.* (8) who were able to demonstrate, by means of polarizing microscopy and SEM, that structures primarily composed of weddellite crystals may convert into whewellite by a dissolution-recrystallization process.

These crystalline changes are important to be considered because they explain the polymorphism of some stone components. Also they account for the great

Figure 8. Type IIIa calculi. Color: orange. **8a**. Smooth surface. Composition: pure anhydrous uric acid. Dimensions: 4 x 4 x 3.5 to 9 x 8 x 8 mm. **8b**. Cross-section made of concentric layers with radial crystallization. Composition: uric acid anhydrous (95%) + uric acid dihydrate (5%). Dimensions: 34 x 30 x 25 mm.

Figure 9. Type IIIb stone. **9a**. Heterogeneous embossed, rough and porous surface. Color: whitish to brownish-red. Composition: uric acid anhydrous (75%) + uric acid dihydrate (25%). Dimensions: 42 x 37 x 30 mm. **9b**. Unorganized and porous cross-section. Color: red-orange. Composition: uric acid dihydrate (65%) + uric acid anhydrous (35%). Dimensions: 18 x 12 x 8 mm.

Figure 10. Type IIIc stone. Rough and porous surface. Color: whitish to grayish. Composition: pure calcium hydrogen urate hexahydrate. Dimensions: 11 x 10 x 9 mm.

Figure 11. Type IIId stone. **11a**. Rough and extensively porous surface. Color: grayish-brown. Composition: ammonium hydrogen urate (95%) + whewellite (5%). Dimensions: 20 x 12 x 9 mm. **11b**. Heterogeneous section with porous concentric layers. Color: beige to pink-brown. Composition: ammonium hydrogen urate (90%) + whewellite (10%). Dimensions: 16 x 13 x 10 mm.

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differences observed in the frequency of some crystalline species between stones and crystalluria (139). Moreover, these crystalline conversions explain the possibility to observe, at the microscopic level, a weddellite morphology and to identify whewellite as the main component by physico-chemical methods. As a consequence, the relationships between stones and etiopathogenic factors must simultaneously take into account the stone morphology with the crystalline composition.

Such a classification, based on both morphologic examination and structural analysis of stones, has recently been proposed by Leusmann (76). Attempts to correlate composition of stones with etiopathogenic conditions have been presented by several authors (100, 102, 103, 124, 142).

Proposed Morphoconstitutional Classification

Analytical procedure

In routine analysis, we first examine the surface and the section of the calculi by means of a dissecting microscope. This is a simple and convenient way to obtain all the clinically useful information on the main compounds and structure of the stone. This technique permits us to
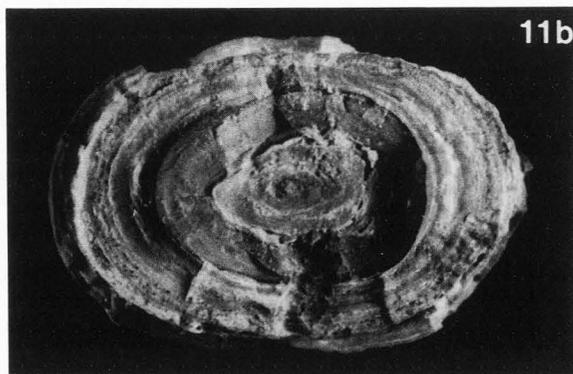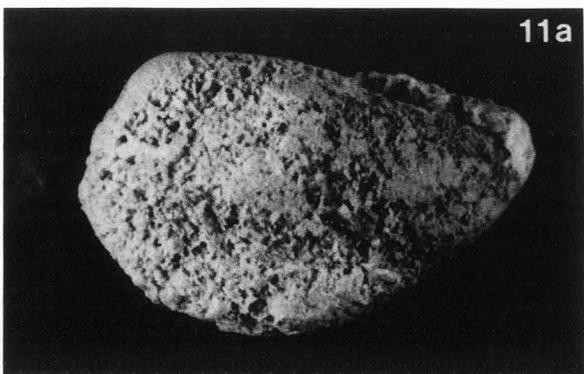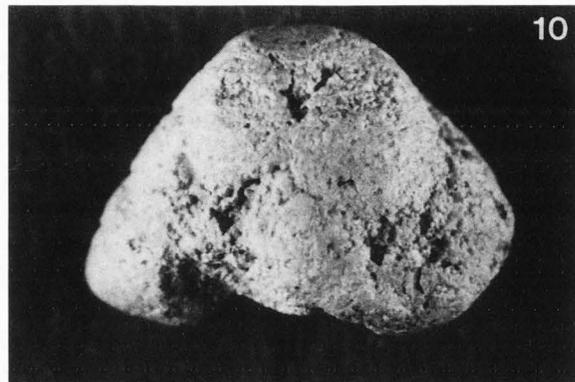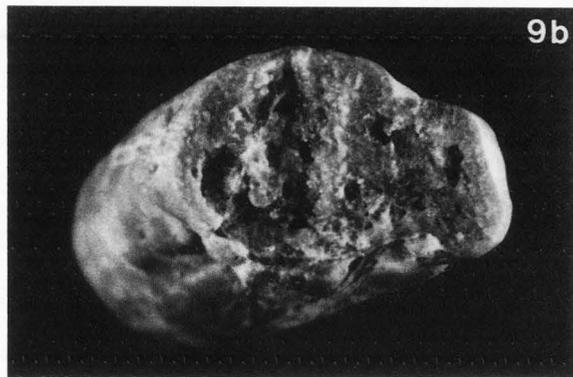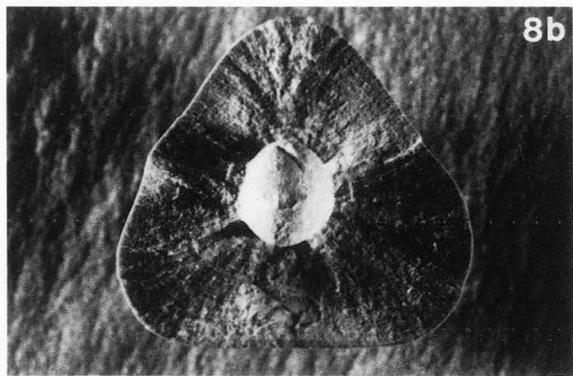
detect the presence of a Randall's plaque as nucleus of the stone, one or several bracketing sides suggesting that other calculi were present in the same caliceal area. Signs indicative of stone activity are noted as bright color for whewellite structures, shapes and sizes for weddellite crystals or pigmentation of CaP stones. After having recorded surface characteristics, the calculus is sectioned using a scalpel and cross-sections are examined. The radial or/and concentric structure is noted. The nucleation area is localized from the orientation of the crystallization planes on cross-sections by looking at two or if necessary several cuttings of the stone.

Although surgical procedures are now restricted to some difficult cases and replaced by new non-invasive techniques such as extracorporeal shock wave lithotripsy (ESWL), analysis of stones or fragments should not be neglected and still remains a prominent part of etiologic investigation of the lithiasic patient. Fortunately, even small fragments passed following ESWL still afford valuable information when properly analyzed (34). The morphological typing can still be performed but the nucleation area is lost in a great number of cases (up to 50% of the stones).

In a second step, a sample of each significant part of the stone (nucleation area, section, surface) is taken off using the microscope and analyzed by IR spectroscopy. The relative amount of the stone components is obtained by studying a sample of a powder from the whole stone.

Using this protocol, we analyzed more than 10,000 urinary calculi over the last 10 years. Based on the combined information provided by microscopic and IR analysis, we developed a morphoconstitutional classification of urinary stones. Seven main types and 21 subtypes were thus defined which can be related to crystalline composition. Furthermore, in most cases, using clinical and biological data, strong and specific correlations between the various stone types and subtypes, and the corresponding etiopathogenic conditions of stone formation, could be established.

Description of the morphoconstitutional types and subtypes

Since observation of the superficial and internal structures of the stone and recognition of the morphology of a number of crystals make possible to identify the main components which are present by simple microscopic examination, we tried to establish codified relationships between composition and structure by observations of both surface and cross-section of calculi under a low magnification (x10 to x100) using a dissecting microscope. We classified stones into 7 main types with regard to the composition, subdivided into 21 subtypes: type I for whewellite stones, type II for weddellite

stones, type III for uric acid and urate stones, type IV for calcium and magnesium phosphates, type V for cystine stones, type VI for protein-rich calculi (31, 39), and type VII for miscellaneous specific stones (dihydroxyadenine, xanthine, drug stones, etc.). Morphological characteristics of each type are given in Table 1 and illustrated in Figures 1 to 21. Some examples of mixed types are shown in Figures 22 to 27.

The main advantages of such morphoconstitutional classification are: more than 95% of the urinary calculi fall into one of these groups, of which, each corresponds to a peculiar set of structural characteristics; and each morphological type is linked simultaneously with a textural form and with a crystalline component.

Some calculi have a "pure" structure, i.e., have an homogeneous composition with the same morphological type for both surface and section, but in most cases a modification is apparent from the core up to the surface of the calculus, defining a "mixed" structure.

Qualitative and quantitative data allow to classify calculi into the corresponding etiopathogenic categories defined by one or more main lithogenetic risk factors, sometimes specific. Stones that correspond to an unusual composition or morphology induced by unusual lithogenetic factors (42) are put together in type VII.

Relationships between morphoconstitutional classification and etiopathogenic factors

We compared morphology and composition of calculi with blood and urine biochemistry and bacteriology data obtained on the corresponding patients. Main correlations between etiology and morphoconstitutional data are summarized in Table 2 for surface morphology of pure stones, and in Table 3 for surface morphology of mixed stones. Table 4 shows correlations between nucleus and section types and pathophysiologic factors. Some examples are discussed below. The main correlations between etiologic and morphologic types of calcium stones are shown in Table 5. The threshold values for the main urine biochemical lithogenic factors in stone formers as defined in our laboratory are represented in Table 6.

Formation of type I calculi, with whewellite as the main component, mainly depends on high oxalate urinary concentration, whatever the specific cause of hyperoxaluria (50, 51, 53), whereas type II calculi, with weddellite as the main component, almost always are associated with hypercalciuria, either absorptive, resorptive or renal.

Type IIIa or IIIb stones imply urinary uric acid supersaturation, resulting either from hyperuricosuria or from low urine pH, whereas type IIIc or IIId stones rather are formed in alkaline or weakly acid urine with, usually, a high renal ammoniagenesis.

Table 4. Correlations between the main types of nucleus and
section of calculi and corresponding pathophysiologic factors.

Type of Nucleus	Type of Section	Main Etiologic Conditions
Ia	Ia, Ia + IVa	Hyperoxaluria; medullary sponge kidney.
Ia, Ib	Ia, Ib, Id, IIa	Hyperoxaluria.
Ic	Ia, Ic	Primary hyperoxaluria.
IIa, IIb, IIc	IIa, IIc	Hypercalciuria.
IIb	IIb	Hypercalciuria, hyperoxaluria; stasis.
IIa, IIb	IIa + IVa (unorganized or concentric)	Hypercalciuria, primary Hyperparathyroidism.
IIIa	IIIa	Low urinary pH; stasis.
IIIb	Ia, IIIa, IIIb	Hyperuricosuria and/or low urinary pH.
IIIc	IIIb, IIIc	Hyperuricosuria + high urinary pH. Hyperuricosuria + low phosphate intake.
IIIc	IVc	Hyperuricosuria + infection with urease-producing organisms.
IIIc	Ia	High urinary sodium urate concentration.
IIId	Ia, IIId	Infection with urease-producing organisms; malnutrition; anorexia nervosa; hyperammoniagenesis (low phosphate intake); laxative abuse.
IVa	Ia	Randall's plaque; Medullary sponge kidney.
IVa	IIa, IIb, IIa, IVa	Hypercalciuria; primary hyperparathyroidism.
IVa	IVa, IVb, IVc	Urinary tract infection.
IVa	Ia + IVa	Medullary sponge kidney.
IVa	IVa2	Renal tubular acidosis.
IVa, IVd	IVd	Hypercalciuria; primary hyperparathyroidism; uropathy; renal tubular acidosis; renal phosphate leak.
IVc	IVa, IVb, IVc	Infection with urease-producing organisms.
Va	Va, Vb	Cystinuria
VIa	VIa	Urinary tract infection (usually with urease-producing and proteolytic enzyme-producing organisms).
VIb	Ia, Ib, Id, IIb, IIIb, VIb VIb	Proteins; clots; drug-induced calculi. End-stage chronic renal failure.
VIc	VIc	End-stage chronic renal failure; chronic dialysis.
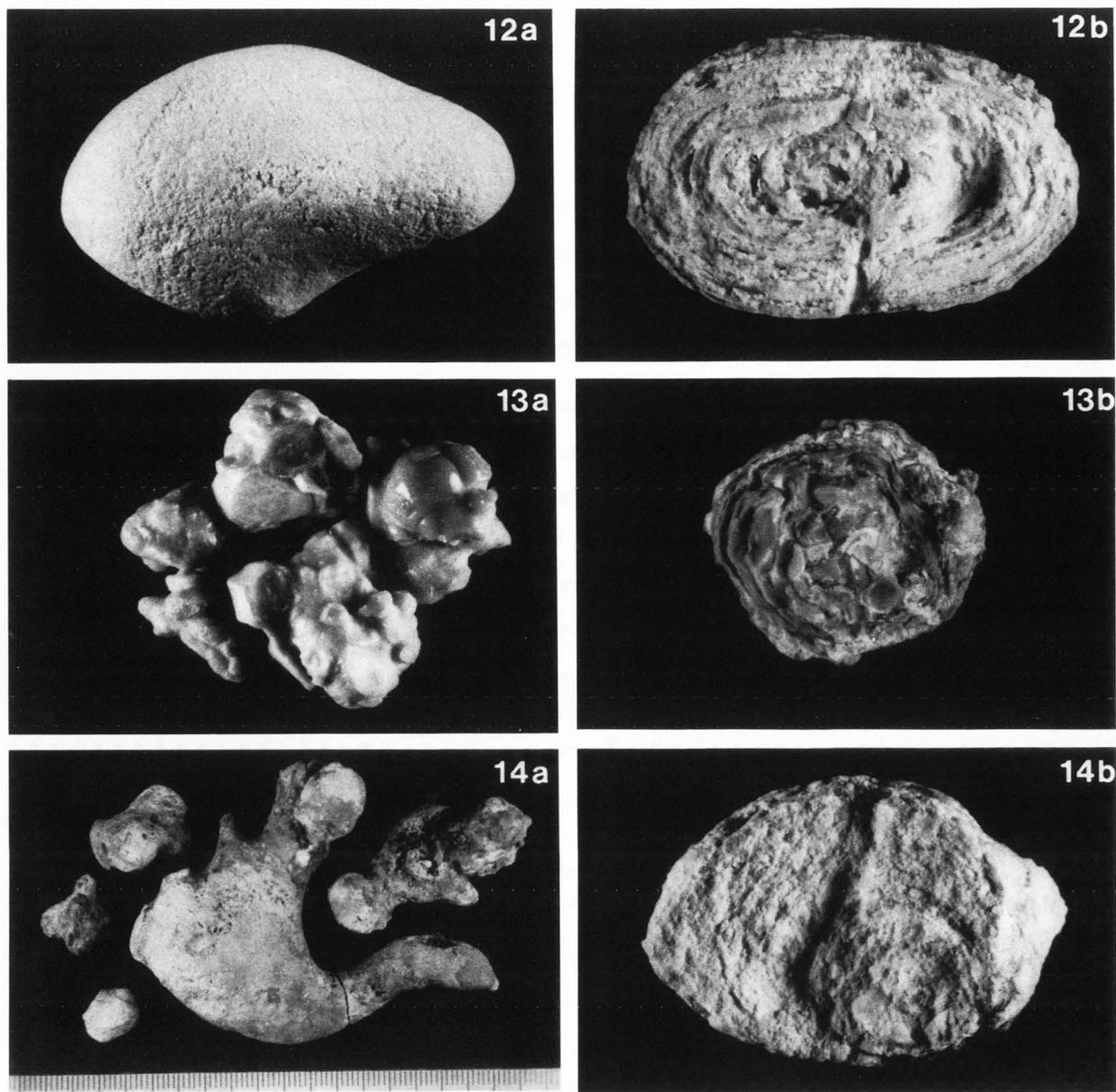
Figure 12. Type IVa (IVa1) stone. **12a**. Homogeneous rough surface. Color: beige. Composition: carbapatite (75%) + carbonated amorphous calcium phosphate (15%) + struvite (10%). Dimensions: 28 x 22 x 18 mm. **12b**. Cross-section with diffuse concentric structure. Color: whitish to beige. Composition: carbapatite (70%) + carbonated amorphous calcium phosphate (20%) + calcium oxalate monohydrate and dihydrate (5%) + proteins (5%). Dimensions: 15 x 10 x 8 mm.

Figure 13. Type IVa2 stones. **13a**. Smooth surface with glazed appearance and cracks. Note the multiple joining faces between the stones. Color: brown-yellow. Composition: carbapatite (97%) + proteins (3%). Dimensions: 5 x 5 x 4 to 9 x 8 x 7 mm. **13b**. Heterogeneous section with concentric foliated structure. Color: beige to brown-yellow. Composition: carbapatite (85%) + carbonated amorphous calcium phosphate (12%) + proteins (3%). Dimensions: 8 x 7 x 6 mm.

Figure 14. Type IVb stones. **14a**. Staghorn calculi. Heterogeneous, both embossed and rough, surface. Color: beige to brown-yellow. Composition: carbapatite (70%) + struvite (30%). Dimensions: 10 x 8 x 7 to 70 x 55 x 28 mm. **14b**. Heterogeneous section with alternate concentric layers. Color: whitish to brown-yellow. Composition: carbapatite (65%) + struvite (34%) + ammonium hydrogen urate (1%). Dimensions: 60 x 20 x 17 mm.
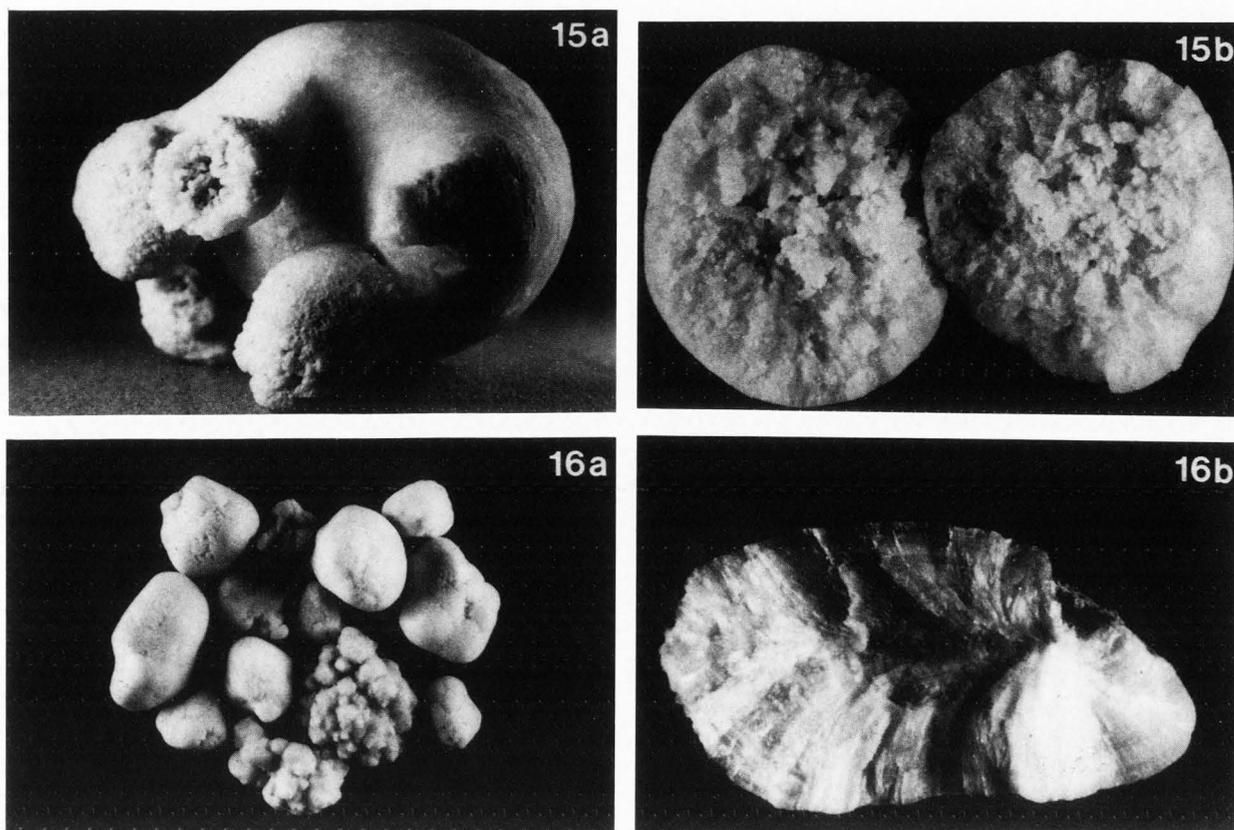
Figure 15. Type IVc calculus. Color: whitish. **15a.** Homogeneous surface composed of amalgamated large crystals. Composition: struvite (90%) + carbapatite (10%). Dimensions: 110 x 95 x 90 mm. **15b.** Unorganized cross-section made of aggregated crystals. Composition: struvite (95%) + carbapatite (5%). Dimensions: 13 x 13 x 12 mm.

Figure 16. Type IVd stones. Color: beige. **16a.** Finely rough or dappled surface. Composition: brushite (74%) + carbapatite (24%) + weddellite (1%) + whewellite (1%). Dimensions: 6 x 5 x 4 to 10 x 9 x 8 mm. **16b.** Cross-section made of concentric layers with radial crystallization. Composition: pure brushite. Dimensions: 13 x 13 x 7 mm.

Type IV stones have in common to be formed in urine of which pH is permanently above 5.8, as a result of defective tubular acidification (metabolic or infectious in origin), or of ammonia formation by urea-splitting organisms.

Within each main type, subdivision into various subtypes allows us to refine correlations with corresponding lithogenetic risk factors and, in some instances, to assign a given calculus to a specific etiology as discussed below.

Calculi with calcium oxalate as the main component

Type I calculi, purely or mainly made of whewellite, suggest high urine oxalate concentration without hypercalciuria as the main pathophysiologic factor (40). Within this group, Ia subtype is often associated with presence of either a Randall's plaque or tubular ectasias in medullary sponge kidney (MSK), both conditions known to induce intratubular formation of calculi. In our experience, 18% of calculi formed by patients with MSK belong to the Ia morphologic type. However, the major characteristic of calculi in MSK patients was polymorphism. By contrast with other lithogenetic diseases, stones passed simultaneously or successively by a MSK patient were in nearly 70% of cases heterogeneous in structure and differed from one another, variably combining types I, II and IV (66). Sometimes, Ia subtype is associated with combined mild hyperoxaluria and hyperuricosuria. As previously reported, such patients can develop stones due to alteration of urinary glycosaminoglycans induced by uric acid or monosodium urate (24, 104).

Calculi of Ic subtype were always associated, in our experience (39 cases), with primary hyperoxaluria type I. This very specific relationship between stone type and pathology is of great clinical interest to early detect this severe metabolic disorder. On the other hand, even when recurrent and multiple, type I calculi of a, b, c or

d subtypes never were associated with primary hyperparathyroidism and in our opinion virtually preclude hyperparathyroidism as the lithogenetic condition.

Calculi formed by patients with primary hyperparathyroidism almost constantly are of the morphologic types IIa + IVa, IVa or IVd (Table 5), which usually correspond to a combination of CaOx (in the form of weddellite) and of CaP (carbapatite or brushite). Nearly half of stones have a laminated structure with alternate layers of CaOx and CaP while other stones show unorganized cross-sections with clusters of weddellite crystals intermixed with carbapatite deposits. Our findings are in good agreement with observations of Cifuentes et al. (22) on the structure and composition of calculi in patients with primary hyperparathyroidism. When a calculus contains less than 5% CaP, the likelihood of primary hyperparathyroidism is very low. The usually high content in CaP can be explained by the frequent simultaneous occurrence of hypercalciuria and hyperphosphaturia, but also by the moderate increase of urinary pH induced by the bone catabolism as demonstrated by Nordin (93) and by Coe (25). Such rise in urinary pH is not found in all patients with hyperparathyroidism, thus explaining that some patients produce calculi mainly composed of CaOx. Obviously, quantitative analysis of components is of significance only if studied samples are representative of the whole calculus.

Calculi with calcium phosphate as the main component

Within the type IV group, type IVa2 morphology deserves special attention. In our experience, such morphology specifically suggests an acidification defect, due either to primary complete distal tubular acidosis or to Sjögren's syndrome. Both conditions were associated with type IVa2 stones in 90% of our cases. Two other possible etiologic conditions are intratubular stone formation in MSK with medullary nephrocalcinosis and acidification defect, and chronic renal parenchyma infection resulting in altered tubular acidification. In our series, about 8% of stones formed by MSK patients belong to the IVa2 subtype.

Of note, tubular ectasias (in MSK) or chronic pyelonephritis usually do not affect all nephrons in a homogeneous fashion. In a number of cases, part of nephrons are spared and when the number of intact nephrons is sufficiently high, their normal functional capacity compensates for the defective tubular acidification of altered nephrons, so that no impaired acidification capacity is apparent in the final urine (63), at least when using usual investigation techniques, which reflect the functional capacity of whole kidney mass. Therefore, only extended diffuse tubular alterations can be detected by laboratory tests. However, as type IVa2 calculi may result

Figure 17. Type Va stone. Color: yellow-brown. Composition: pure cystine. **17a.** Granular surface. Dimensions: 30 x 21 x 13 mm. **17b.** Section with crude and diffuse radial structure. Dimensions: 25 x 17 x 10 mm.

Figure 18. Type Vb calculi. **18a.** Smooth surface. Color: pale yellow-brown. Composition: cystine (97%) + carbapatite (3%). Dimensions: 7 x 6 x 5 to 12 x 10 x 8 mm. **18b.** Heterogeneous section with microcrystalline thin concentric layers in periphery and an unorganized crystalline core. Color: beige to pale yellowbrown. Mean composition: cystine (98%) + carbapatite (2%). Dimensions: 3 x 3 x 2.5 to 5.5 x 5 x 4.5 mm.

Figure 19. Type VIa calculi. Mucoprotein matrix. Color: brown-yellowish. Composition: pure mucoprotein. Dimensions: 55 x 40 x 30 mm.

Figure 20. Type VIb stone. **20a.** Smooth, rough and crackled surface. Color: pale brown. Composition: carbapatite (50%) + proteins (25%) + carbonated amorphous calcium phosphate (15%) + struvite (10%). Dimensions: 16 x 11 x 8 mm. **20b.** Cross-section with crude, foliated and crackled concentric structure. Color: yellow and dark brown. Composition: free glaphenic and hydroxyglaphenic acids (65%) + proteins (35%). Dimensions: 18 x 15 x 12 mm.

Figure 21. Type VIc stones. Smooth and crackled surface. Color: dark brown to black. Unorganized cross-section made of small agglomerated crystals pale yellowbrown in color. Composition: whewellite (65%) + proteins (35%). Dimensions: 0.8 x 0.8 x 0.7 to 5 x 3.5 x 3 mm.

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from focal nephron involvement such as in MSK, presence of such calculi is highly suggestive of an underlying distal acidification defect, either focal or diffuse, and either congenital or acquired.

Uric acid and urate stones

IIIa and IIIb subtypes correspond to uric acid stones. The former is mainly observed in stasis conditions such as prostatic adenoma. Conversely, the IIIb subtype is encountered in all contexts where uric acid supersaturation exists, such as, permanently low urine pH or hyperuricosuria. IIIc subtype is mainly observed in patients with hyperuricosuria and alkaline urine due to therapy. Aluminum magnesium complex urate encountered in hemodialyzed patients treated with aluminum hydroxide belongs to this subtype (32). Another context is ammonium urate supersaturation induced by hyperuricosuria and simultaneous UTI by urea-splitting bacteria.
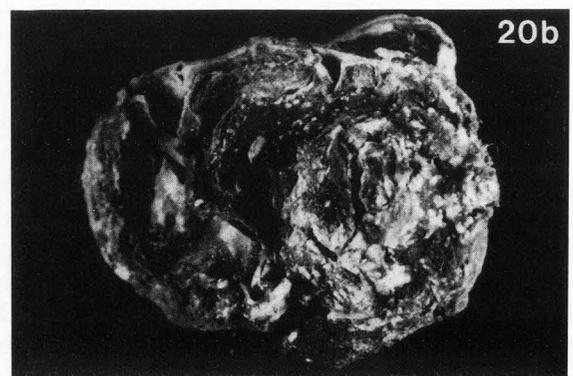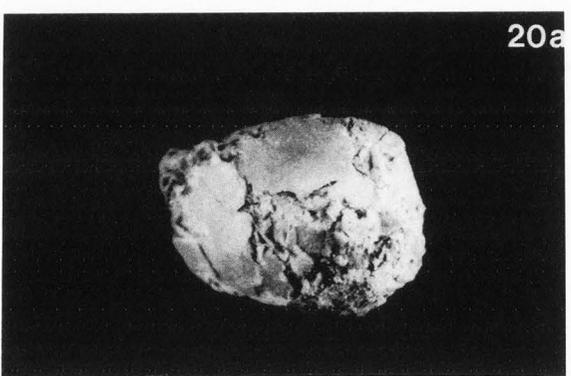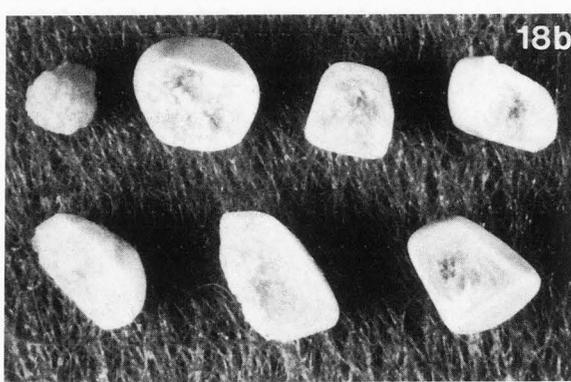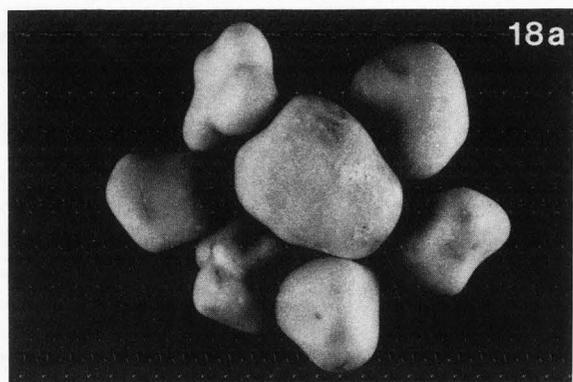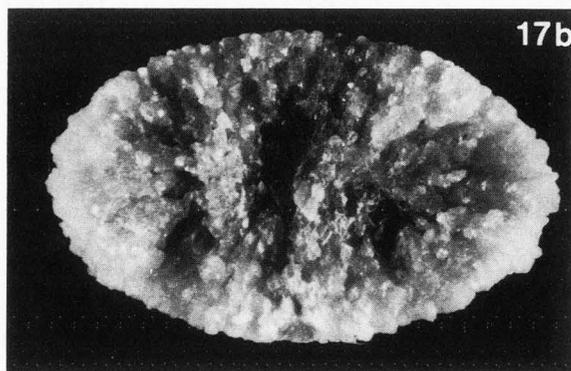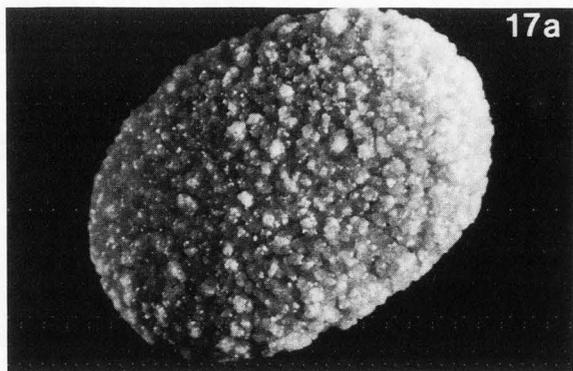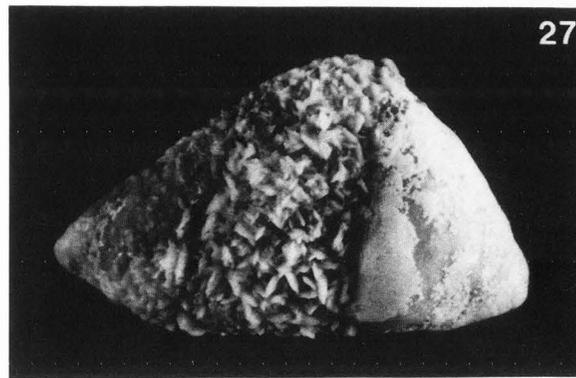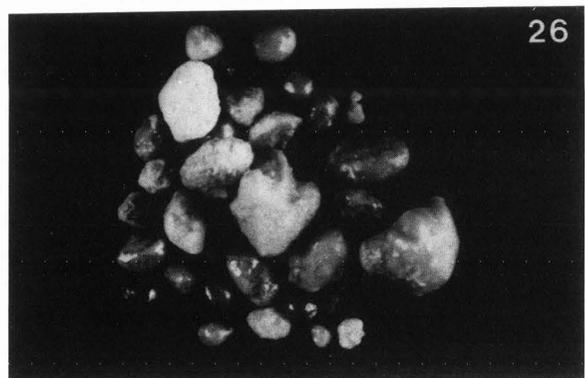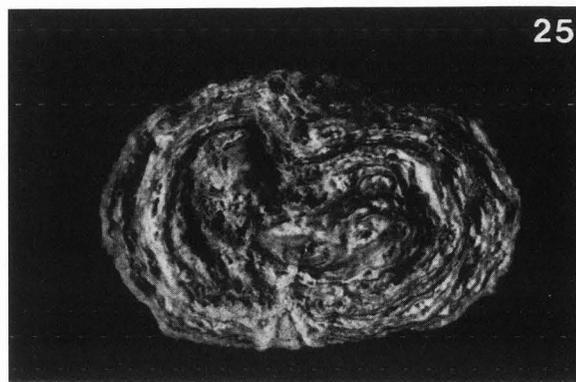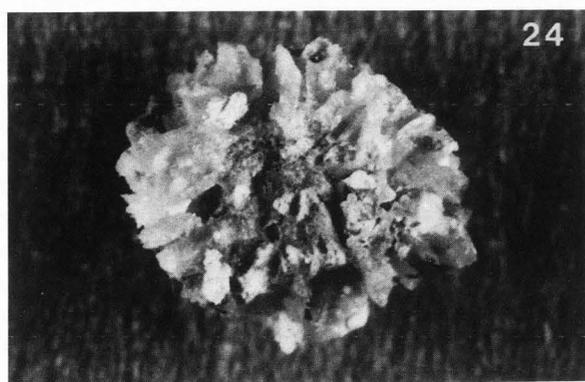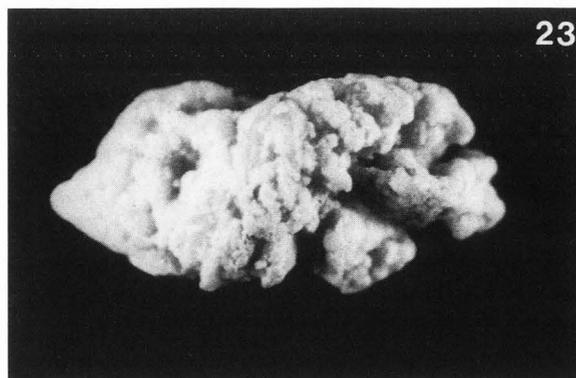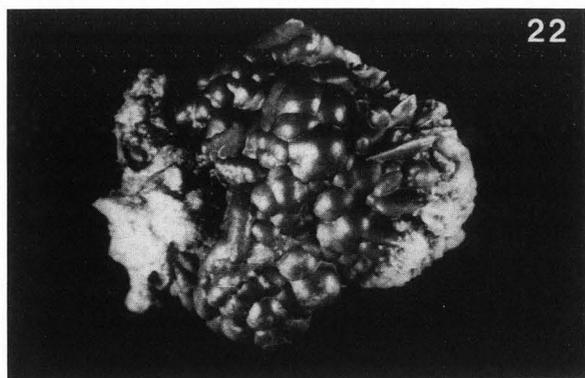
Figures 22 to 27: Some examples of morphological associations.

Figure 22. Example of type Ia + type IIa association. Composition: whewellite (90%) + weddellite (10%). Dimensions: 18 x 16 x 13 mm. **Figure 23.** Mixed stone with type IVa + IIa structure. Composition: weddellite (45%) + carbapatite (40%) + whewellite (15%). Dimensions: 8 x 4 x 3 mm. **Figure 24.** Type IIa + IVa mixed stone. Cross-section with some scattered deposits composed of carbapatite. Composition: weddellite (86%) + carbapatite (9%) + whewellite (5%). Dimensions: 11 x 10 x 6 mm. **Figure 25.** Another section of a type IIa + IVa mixed stone. Note the concentric structure with alternated irregular layers. Color: beige to brown-yellowish. Composition: weddellite (50%) + carbapatite (40%) + whewellite (10%). Dimensions: 15 x 11 x 8 mm. **Figure 26.** Heterogeneous morphology of multiple stones spontaneously passed in a patient with medullary sponge kidneys. Mean composition: carbapatite (50%) + whewellite (30%) + whitlockite (10%) + weddellite (10%). Dimensions: 0.6 x 0.6 x 0.5 to 4 x 4 x 3 mm. **Figure 27.** Example of an heterogeneous calculus with mixed type Ia (left side) + IIa (medium area) + IIIb (right side). Color: beige to dark brown. Composition: uric acid anhydrous (35%) + whewellite (25%) + uric acid dihydrate (20%) + weddellite (20%). Dimensions: 28 x 20 x 16 mm.

Table 5. Correlations between etiologic conditions and morphologic types of calcium stones.

Patho-Physiologic Conditions	Number of Patients	Oxalate as Main Component (%)	Surface Morphologic Type (%)				
			I	I+II	II	II+IV	IV
Hypercalciuria	249	81.6	0.4	8.8	61.1	28.1	1.6
Hyperoxaluria	135	100	97.7	1.5	0	0.8	0
Hypercalciuria + hyperoxaluria	54	100	13.0	72.2	11.1	3.7	0
Primary hyperparathyroidism	55	45.4	0	0	11	58.2	30.8
Medullary sponge kidney	125	79.2	24.8	33.6	7.2	16.8	17.6

Table 6. Threshold values of main urine biochemical compounds in stone formers.

	Metabolic abnormalities (mmol/24 h)		Risk of stone formation (mmol/l)
	Males	Females	both sexes
Hypercalciuria	> 7.5	> 6.0	> 3.8
Hyperoxaluria	> 0.45	> 0.45	> 0.3
Hypocitraturia	< 1.5	< 1.7	< 1.0
Hyperuricosuria	> 4.8	> 4.2	> 2.5
Hyperphosphaturia	> 36.0	> 32.0	> 24.0

IIId subtype is encountered in peculiar pathologic contexts such as low phosphate intake with or without infectious diarrhea (endemic lithiasis), laxative abuse and all conditions of high renal or urinary ammonia synthesis.

Cystine stones

The Va subtype stones show a granular and embossed superficial morphology and correspond to recently formed or untreated stones. A different appearance, smooth or very finely rough, is observed in cystine stones formed during alkaline therapy. These stones incorporate in their peripheral layers some proportions of CaP and the cystine crystals are often of reduced size as compared to non-treated patients. Consequently, these cystine stones have a modified morphology corresponding to the Vb subtype (Fig. 18). Two morphological subtypes of cystine stones have also been recently observed by Bhatta et al. (10).

Protein stones

All the protein-rich stones are included in the VI type that was split into three subgroups according to their structure and cause. The VIa subtype includes all soft matrix encountered in pyelonephritis. The VIb subtype includes stones induced by different pathogenic factors such as lithogenetic drugs, pyelonephritis, or metabolic disorders. The VIc subtype is specific to stones developed in hemodialyzed patients receiving associated treatments such as calcium or vitamin D supplementation. In hemodialyzed patients, the high tubular content of proteins like albumin and β-2-microglobulin may lead to the formation of calculi mainly composed of proteins admixed with whewellite crystals. Conversely, first crystallization of whewellite can be responsible for stones which secondarily incorporate protein material (32).

Miscellaneous stones

Stones grouped in type VII correspond to calculi with specific morphology and composition such as xanthine stones induced by xanthine oxidase deficiency and dihydroxyadenine stones induced by adenine phosphoribosyl transferase defect (18). Drug-containing stones such as phenazopyridine, oxypurinol, silica and calcite stones are also included in this group.

Conclusions

Proper analysis of stones requires a combination of microscopical, physical, and chemical methods used in appropriate order and applied to separate analysis of the core, section and surface of the calculus. Combined with microscopic examination, X-ray diffraction analysis, or IR spectrophotometry, permit precise qualitative and quantitative determination of the morphology and composition of calculi.

We propose a "morphoconstitutional" classification of urinary calculi based on the combination of morphologic and compositional analysis. Correlations between the different types and subtypes of stones and the corresponding etiopathogenic conditions most frequently observed in our patients are presented. In view of the correlations found between stone analysis and etiologic factors, careful morphologic and constitutional analysis of urinary stones should not be neglected. Typological classification of urinary stones as described in the present paper is able to constitute a prominent and fruitful part of the etiologic investigation of the lithiasic patients.

Acknowledgements

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Discussion with Reviewers

W.G. Robertson: Do the authors consider it essential to analyse stones in terms of its different parts, i.e., the "nucleus" separately from the rest of the stone? If so, how do they decide on what constitutes the "nucleus"?
Authors: We find it of interest to separately analyze the different parts of stones because composition of the core (or "nucleus") reflects the conditions that initiated stone formation, whereas more superficial parts depend on the physicochemical conditions that were present during stone growth. We define the nucleus as the smallest part of the stone towards which radial striation is convergent or the concentric structure observed on several cross-sections. Of course, when the same lithogenic factors are permanent, stone structure is homogeneous such as in cystinuria

or primary hyperoxaluria. By contrast, composition of core may differ from that of more superficial parts. As examples, a core made of uric acid surrounding by whewellite layers is indicative of heterogeneous nucleation of CaOx upon uric acid as inductor; a core made of CaOx surrounded by calcium and magnesium phosphates layers indicates initial presence of metabolic disorder such as hypercalciuria and/or hyperoxaluria and subsequent growth by urea-splitting microorganisms infection; and a core made of CaOx with weddellite structure surrounded by CaP is suggestive of hypercalciuria associated with primary hyperparathyroidism or tubular acidification defect. A number of spontaneously passed whewellite stones (Ia subtype) developed from a CaP deposit (Randall's plaque), which served as a nucleus. In some cases, the initial papillary deposit is made of sodium hydrogen urate.

W.G. Robertson: How would the authors recommend the analysis of stones greater than (say) 2 mm diameter? Would they pulverize the whole stone and sample part or all of the complete mixture or would they sample only part of the stone before analysis?

Authors: The method of stone analysis is essentially the same whatever the stone size. We always analyze the morphology of surface and of section of the stone, looking at identifying the nucleus as defined above, and we take with a needle a sample of the core and of several surrounding areas. When this is done, the whole stone (if small), or a representative sample is disintegrated for IR spectroscopy analysis in order to quantify the respective proportions of stone components.

H.G. Tiselius: The delicate problem of determining the composition of the nucleus as well as the remaining part of the stones is difficult today because of the new technology that results in gravel and no large unaffected stones. What is your suggestion for analysis of the disintegrated stone?

Authors: At the present time, a frequent situation is that only small fragments passed after ESWL or percutaneous nephrolithotomy are available for analysis. Nevertheless, accurate information can still be obtained from analysis of such fragments. By means of microscopic analysis of fragments with binocular lenses, structure and morphological type of the stone could be identified in nearly 90% of cases in our experience (ref. 32). In addition, a nucleus could be recognized in about half of cases. In such cases, analysis of the different parts of the calculus may be proceeded as for whole stones. When only scarce very small fragments are available, true composition and morphology of the calculus cannot be reconstructed. In this case, the fragments can be converted into powder for IR analysis to obtain some information about the composition.

H.G. Tiselius: Would it, from your vast experience, be possible to describe stone composition by careful examination of the radiographic appearance of the concrement possibly in association with some information on urine composition?

Authors: Identifying stone composition from its radiographic appearance is a much debated concern. Well-known considerations on radiolucent stones will not be recalled, although not only uric acid but several types of endogenous or iatrogenic stones may be responsible for such an appearance; characteristic and specific crystalluria is often found in such cases, such as presence of 2,8-dihydroxyadenine crystals. With regards to X-ray opaque stones, the type of calcium component may only be suspected on the basis of roentgenologic appearance. Weddellite stones often have a finely spiculated outline, whereas whewellite and phosphate stones have a more regular and clear-cut contour; an umbilicated structure is sometimes apparent, highly suggestive of a whewellite stone. Multiple, small calculi with a precaliceal situation are suggestive of medullary sponge kidney but also of other causes of medullary nephrocalcinosis. In all such cases, blood and urine chemistry as well as crystalluria provide more important etiopathogenic indices than roentgenologic appearance of stones.

Presence of uric acid, cystine or struvite crystals is indicative per se, respectively of uric acid stones, cystinuria or infection with urease-producing organisms. Presence of monohydrate or dihydrate crystals is suggestive of a corresponding composition of stones, i.e., monohydrate or dihydrate CaOx. In fact, crystalluria and biochemical data provide information about recent lithogenetic factors, but not necessarily about the factors that were involved at the time of nucleation and growth of the calculus.

H.G. Tiselius: Are there any technical possibilities available today or discernible at the horizon that might make *in situ* analysis of stone composition possible?

Authors: In a very near future, *in situ* analysis of stone composition should be available using Raman Laser fiber optics spectroscopy by means of optical fibers inserted in an ureteroscope or a nephroscope and placed in contact with the stone. Preliminary studies have been published (92).

B. Hess: What evidence can the authors provide for the reproducibility of their method, i.e., if several investigators from different independent laboratories were to analyze a group of stones according to the proposed classification system, would they obtain identical results?

Authors: We evaluated reproducibility of our method by testing results of analysis of various stones according to our proposed morphoconstitutional classification performed by 25 investigators from 12 different laboratories.

Following a three-day full time training, providing an experience based on at least 150 stones including all types and subtypes, nearly all trained physicians or laboratory technicians were able to properly identify and classify more than 95 % of all examined stones in accordance with our classification. Especially, all trained investigators were able to recognize the Ic and IVa2 subtypes which are virtually specific of primary hyperoxaluria and distal tubular acidosis in our experience. Such information is not provided by IR or XRD analysis.

Thus, we can state that the proposed classification, although it may appear complex at first inspection, is in fact, easy to learn and very reproducible. Furthermore, the more detailed the classification, the more specific the correlation with physicochemical etiopathogenic factors.

J.R. Asplin: How does this morphologic classification change the approach to therapy in the patient? Would you expect stone therapy to be more effective with therapy directed by etiologic factors as determined by morphology rather than by urine chemistries as is done now?
Authors: The morphologic classification is not primarily aimed at providing rules or algorithms for the choice of therapy. However, stone therapy must be based not only on urine chemistry but, primarily, on the etiologic conditions as defined from clinical and biological investigations including stone analysis. From this point of view, such refined classification of stones may permit (or strongly suggest) immediate identification of specific conditions, such as, primary hyperoxaluria (type Ic), distal tubular acidosis either complete or incomplete (type IVa2), primary hyperparathyroidism (type IVa1 or mixed morphology IVa1 + IIa), or sometimes unusual lithogenetic conditions, out of the vast group of CaOx or CaP stones. Moreover, as a result of the refined classification orientation to more specific laboratory examinations can be advise. In most of these cases, XRD or IR spectroscopy of whole stones would only identify CaOx monohydrate or carbapatite without further approach to specific etiologic factors. With regard to the most frequent types of CaOx stones, a type Ia morphology suggests intermittent, mild hyperoxaluria. This condition is frequently associated in our experience to low diuresis and such finding emphasizes the need for serial urinary density measurements and recommendations for sufficient and well-distributed fluid intake throughout the nycthemer. As another example, more than 100 cases of whewellite stones referred to our laboratory exhibited an unusual morphology. Etiological inquiry allowed us to relate these stones to piridoxilate treatment (40). Consequently, piridoxilate treatment was stopped and replaced by another drug without hyperoxaluric effects. These examples emphasize the need for stone therapy to be based on a comprehensive etiopathogenetic approach in which morphoconstitutional analysis plays a prominent part.

J.R. Asplin: In Table 2, hypocitraturia is not listed as an etiologic condition, and hyperuricosuria as a cause of CaOx stones is listed only secondarily with hyperoxaluria. Since effective stone therapy is often aimed at these two metabolic abnormalities, how do you think they fit in with this morphologic characterization of kidney stone disease?
Authors: That hypocitraturia and hyperuricosuria are not listed as single etiologic conditions for CaOx stones is based on the fact that such metabolic disturbances have not been found as independent single pathogenic factors in any type of CaOx stones in our experience. When a marked, permanent hypocitraturia was present, it was constantly associated with another condition such as tubular acidifying defect, enteric hyperoxaluria or occult diarrhoea, with the corresponding morphoconstitutional types of stones. Similarly, with regard to pure CaOx stones, none of the seven proposed subtypes correlated with hyperuricosuria as the single lithogenic factor. In our calcium stone formers, hyperuricosuria was nearly always associated with some degree of hypercalciuria, hyperoxaluria, low urinary pH, or low urinary output. Even in cases of mixed urico-calcic stones, hyperuricosuria was sometimes lacking and hypercalciuria or hyperoxaluria was associated with low urine pH responsible for uric acid supersaturation. Moreover, we and others know a number of patients with recurrent CaOx stones treated with allopurinol because of hyperuricemia and/or hyperuricosuria. This treatment has been ineffective to reduce stone activity due to persistent mild hyperoxaluria. Thus, on the basis of our present experience, neither hypocitraturia nor hyperuricosuria acted as single, independent factors for CaOx stone formation and, therefore, cannot be ascribed to a specific subtype. Obviously, this does not, in any way, preclude the need for correcting hypocitraturia and/or hyperuricosuria when they contribute to the risk of CaOx crystal formation and/or aggregation.

As a final comment, we propose that the detailed morphoconstitutional classification described here constitutes a part of the evaluation of the urolithiasis patient, in combination with (and not exclusive of) data provided by blood and urine chemistry determinations. Although apparently complex, stone morphoconstitutional analysis is in fact easy to learn while being highly cost effective. Such a classification provides information in agreement with urine chemistry in the case of common CaOx stones and frequently gives additional information with regard to the stone activity. Moreover, its interest lies in the immediate identification of peculiar or specific etiopathogenic conditions. Precise classification of stones leads to well-targeted laboratory investigation and, hopefully, to more effective correction of lithogenic factors.