

## Descriptive Human Pathological Mineralogy

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### Abstract

Crystallographic, petrographic, and X-ray powder diffraction analysis of approximately 15,000 samples showed that the most common mineral constituents of human pathological concretions are calcium oxalates (whewellite and weddellite), calcium phosphates (apatite, brushite, and whitlockite), and magnesium phosphates (struvite and newberyite). Less common are monetite, hannayite, calcite, aragonite, vaterite, halite, gypsum, and hexahydrate. Of the variables determining which minerals precipitate, the effects of different pH values on depositional conditions are most apparent, and are shown by occurrences and relationships among many of the minerals studied. A pH-sensitive series has been identified among magnesium phosphates in concretions.

### Introduction

The importance of mineralogy in the field of medicine lies in the application of mineralogical methods to study pathological mineral deposits in the human body. Urology benefits greatly because concretions of mineral matter (calculi) are common in the urinary system. The value of mineralogical analysis of urinary material was first described by Prien and Frondel (1947). Mineralogists may be unaware of the variability and nature of such compounds because reports are usually published in medical journals. This investigation reports the mineralogy and possible pathological significance of these minerals.

Some mineralogists would not consider these materials minerals in the strictest sense. Because most of these compounds are identical with minerals in composition and structure, and often in mechanics of their formation, they are herein referred to by mineral names, leaving the question of their status unanswered. Only those compounds existing elsewhere as minerals, *sensu strictu*, are discussed in detail, even though crystalline organic compounds such as uric acid and cystine occur as urinary calculi.

### Scope and Methods

The writer determined mineralogic composition and depositional sequence for approximately 15,000 human pathological mineral deposits obtained from doctors and hospitals in various parts of the United States, with most samples coming from the Midwest.

The study was carried out over a period of three years. Composition was confirmed by X-ray powder diffraction and polarizing microscopy; sequence was arrived at from considerations of microscopic textural and crystallographic relationships. More than 14,500 samples were derived from the urinary system of kidneys, ureters, bladder, and urethra; the remaining samples are not statistically significant and are discussed only briefly.

### Calcium Oxalates

Whewellite,  $\text{CaC}_2\text{O}_4 \cdot \text{H}_2\text{O}$ , and weddellite,  $\text{CaC}_2\text{O}_4 \cdot 2\text{H}_2\text{O}$ , are very uncommon in the mineral world. However, they both occur abundantly in calculi. Although the two phases are frequently associated in the same calculus, their habits are markedly different and warrant separate discussion.

#### *Whewellite*

The predominant habit consists of smooth to botryoidal or globular, radiating crystalline aggregates. Discrete crystals are rarely present, although a monoclinic (010) or (110) cleavage can be observed in the crystalline mass. The most common colors are brown to olive green, but shades from black to yellow exist. This variation is due to differing amounts of included organic material, including blood. Whewellite calculi very often are deposited upon renal papillae, small protrusions within the kidney. When this happens, the calculus almost invariably has a relatively small nucleus which is

usually composed of apatite, brushite, or whitlockite. Non-papillary whewellite stones also may contain a central apatite core. Both types of stones are concentrically laminated and radial about the nucleus or core, clearly indicating deposition thereon. A special kind of whewellite stone is referred to by urologists as the jackstone, a calculus with symmetrical, elongate, branching protrusions. This preferential growth upon selected sites on the surface of a crystalline aggregate is due to growth imperfections which result from unusual accumulations of organic material. Centers of such branches often show subsidiary nuclei of carbonaceous organic matter.

#### *Weddellite*

In contrast to whewellite, weddellite almost always occurs as well-formed tetragonal dipyrarnidal crystals and aggregates of intergrown single crystals. Colors are also variable, ranging from the common yellow to white or colorless, again reflecting differences in amount of included organic material. Cycles of growth of weddellite crystals are preserved in the crystalline record; secondary and tertiary crops of smaller, differently-colored crystals may be deposited upon the faces of early-formed crystals up to 5 mm on an edge. Occasional super-deposition of whewellite spherules takes place on the apices of weddellite crystals, in the tetragonal prism position. However, most specimens show weddellite following whewellite in depositional sequence. The tetragonal dipyrarnid  $r\{011\}$  is almost unique in weddellite; about 0.5 percent of calculi containing weddellite display tetragonal prisms  $a\{010\}$ , always on yellow crystals, and up to 2 mm across. Much smaller tetragonal prisms were also reported on weddellite by Hutton and Taft (1965).

#### *Pseudomorphism*

Whewellite can form by the partial dehydration of weddellite, resulting in strikingly perfect pseudomorphs. This whewellite occurs as finely granular to coarse, equant prisms. Colorless, yellow, green, and brown varieties exist, sometimes within the same pseudomorph. The replacement of weddellite crystals begins at the center and works outward, becoming increasingly fine-grained. The surfaces of crystals are rarely replaced, probably because contact with the aqueous environment of the urinary system maintains the stability of weddellite. However, weddellite calculi kept in dry sample containers for over five years show no tendency to dehydrate to whewellite.

## Calcium Phosphates

### *Apatite*

The most important mineral in the human body is apatite, the principal mineral constituent of bones and teeth. In urinary calculi two varieties occur: hydroxyl-apatite,  $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ , and carbonate-apatite, in which  $\text{CO}_3\text{OH}$  groups replace  $\text{PO}_4$  in amounts up to 5 percent by weight. Carbonate-apatite is more abundant in calculi than is hydroxyl-apatite, but their habits are the same and both are labeled in what follows as "apatite."

Apatite is the most widespread mineral in calculi. It is associated with most other stone-forming materials, often serving as a center for deposition of subsequent compounds. The first of two important habits for urinary apatite is soft, crumbly, fine-grained, white, yellow, or light brown powder. The second habit is massive, glassy, yellow, brown, or black material. Again, colors other than white are the result of inclusion of organic matter. Both the powdery and glassy varieties are so fine-grained that they appear optically isotropic. Apatite is usually thinly laminated, both in pure apatite calculi and when it occurs as small patches within other mineral frameworks, as in interstices of intergrown weddellite crystals. Glassy apatite sometimes consists of concentric laminations 2-4 microns thick, especially in the rare variety referred to by urologists as "milk of calcium," an unconsolidated mass of spherical stones each less than 1 mm in diameter. Laminations of this material occur on spherulites about one micron across, which give uniaxial optic figures without the aid of condensers or a Bertrand lens.

More common apatite calculi show alternating layers of the powdery and glassy varieties. Prien and Frondel (1947) believed that the glassy laminae "represent a condensation of the substance." While it is possible that surficial powdery apatite could have "condensed" by partial dehydration, dehydroxylation, or even decarbonation, the writer feels that mucus and other organic material adsorbed on the stones' surfaces produce this change in habit. This idea is supported by the action of organic matter as a strong pigmenting agent in most stone minerals, and by the fact that light encrustations of mucus are normally found on the surfaces of many calculi.

### *Brushite*

Isostructural with gypsum, brushite,  $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$ , is much less common than apatite in calculi,

but still occurs regularly. When it does precipitate, it is a response to acidic conditions. Beck (personal communication) has synthesized brushite at pH values of 6.3-6.0. Flat, bladed, colorless-to-yellow monoclinic crystals occur in calculi as radiating aggregates, giving the surfaces of stones a rough, nodular texture. Individual crystals of urinary brushite are tabular on (010), with {001} and {100} also usually present. Small second-order prisms have been noted occasionally. Internally, silky fibers display pearly luster on the perfect (010) cleavage. In four instances brushite was observed in a partial pseudomorphic replacement of laminated, powdery apatite. These calculi also contained later deposits of uric acid, so a change to a more acid-stable phosphate might be expected. However, uric acid and apatite coexist in many calculi.

#### *Monetite*

This triclinic, anhydrous analog of brushite was identified only three times in this group of calculi. Prien and Frondel (1947) reported it in urinary sediments of carnivorous animals. Beck, Mulvaney, and Rhamy (1974) studied the first reported human occurrences, attributing its formation to very low urinary pH (4.13-5.08), naturally buffered urines, and high osmolality. Monetite in the calculi examined by the writer was laminated, gray-to-brown, finely granular material associated with oxalates and apatite. Beck's monetite calculi also displayed lath-like triclinic crystals, and an additional associate was brushite.

#### *Whitlockite*

$\text{Ca}_3(\text{PO}_4)_2$  has long been termed whitlockite, but with recent redefinition of the mineral its formula is now given as *ca*  $\text{Ca}_8\text{Mg}(\text{PO}_4)_6$ . The X-ray pattern of the urinary compound matches that of whitlockite, but adequate chemical analyses are lacking to confirm the presence of magnesium in the urinary material. The following discussion is appropriate whether or not the urinary compound contains essential magnesium.

Whitlockite is unstable in the urinary system; apatite should precipitate instead. However, whitlockite is stabilized in nature by small amounts of magnesium and zinc, and this almost certainly happens in the human body as well. Small amounts of whitlockite sometimes encrust stones containing struvite, a magnesium phosphate, and when associated with apatite, whitlockite forms thick layers,

suggesting relatively long-term changes in the environment such as Mg-enrichment. Finally, pure whitlockite is almost the only constituent of prostatic calculi, and prostatic fluid has the highest concentration of zinc in the human body.

Urinary and prostatic whitlockite has a distinctly resinous luster and a textbook-type hackly fracture. Translucent brown, amber, and yellow laminae are very convolute in section, often clearly illustrating a tendency for small stones to fuse into larger ones. Whitlockite is the only mineral discussed here which regularly shows such fusion. In addition, whitlockite in calculi sometimes has  $\text{CO}_3\text{OH}$  replacement of  $\text{PO}_4$ , as in apatite.

### Magnesium Phosphates

Magnesium phosphates are important indicators of infections in the urinary system. In many cases, the precipitation of the minerals themselves may be enhanced or catalyzed by the presence of the infective organisms. The three urinary magnesium phosphates described here form a pH-sensitive series which is sometimes useful in clinical treatment of calculi; however, buffering and stabilizing effects of infective organisms are poorly understood.

#### *Struvite*

Struvite,  $\text{MgNH}_4\text{PO}_4 \cdot 6\text{H}_2\text{O}$ , is orthorhombic-pyramidal in crystallization. This hemimorphic symmetry is best shown by well-formed, colorless crystals larger than 1 mm across, which display a wide variety of forms. Such crystals line cavities, cracks, and pore spaces in laminated stones composed of powdery apatite co-precipitated with small, white, rounded to blocky struvite crystals. These calculi often develop irregular branches which reach into crevices within the kidney; they are called "staghorns" by urologists and almost always are associated with urea-splitting infections caused by several strains of bacteria. The proportions of apatite and struvite in staghorn calculi vary from  $\text{Ap}_0$  to  $\text{Ap}_{100}$ , but most are in the range  $\text{Ap}_{70}$  to  $\text{Ap}_{30}$ . With increasing struvite content, stones become more porous, and aggregates of struvite crystals assume a columnar, slightly radial arrangement. This change of habit probably reflects the strong effect of centers of nucleation on mode of crystallization, as also seen in the radial habits of whewellite, brushite, hantayite, and some other stone constituents. Although apatite and struvite are usually intimately co-precipitated in human stones, occasional calculi show alter-

nating layers of pure apatite and pure, glassy, densely intergrown struvite crystals.

The infected urines which precipitate struvite are also alkaline. This accounts for the presence of ammonium in this compound, and for its rare association with oxalates, acid calcium phosphates, and uric acid, all of which are stable in more acidic, sterile urines. Struvite is clearly the alkaline end member of the magnesium phosphate pH series in calculi.

### *Newberyite*

A mineralogic enigma is presented by newberyite, an acid phosphate ( $\text{MgHPO}_4 \cdot 3\text{H}_2\text{O}$ ) which is nonetheless frequently associated with struvite and with infections of *Proteus mirabilis*, bacteria known to liberate  $\text{NH}_3$  and thus increase pH by their activity in the urinary system (M. J. Sullivan and R. K. Rhamy, personal communications). However, newberyite is found in calculi in two distinct habits, which may reflect precipitation resulting from bacterial activity as well as precipitation under true acidic conditions.

The most common occurrence of newberyite is as pale-green-to-white, textured spherules scattered on the surfaces and in pore spaces of apatite-struvite stones. Many calculi containing this type of newberyite are crumbly and fragmented, with spherules occurring on broken inner surfaces as well as on exterior portions. The spherules, up to  $2\frac{1}{2}$  mm in diameter, are dense intergrowths of radiating newberyite crystals, and when malformed they exist as rosettes and other splayed forms. Newberyite spherules usually amount to 10–20 percent of a calculus by volume, but in some highly fragmented calculi this proportion may be as high as 90 percent.

Well-formed, vitreous, green, platy, diamond-shaped orthorhombic crystals constitute the second habit of newberyite. Such crystals are smaller than 0.5 mm in length and are found on surfaces of apatite-struvite stones. These calculi are much more consolidated than those containing spherules of newberyite but are otherwise similar. Occasionally, diamond-shaped crystals are so tightly intergrown that they form a thin, coherent shell encrusting all or part of the calculus. A unique and significant exception to the association with apatite and struvite is a uric acid stone encrusted with well-formed diamonds of newberyite as large as 2 mm on an edge. This last instance is evidence for the precipitation of newberyite as the stable magnesium phosphate under acidic conditions in the urinary system.

The association of this acid phase with struvite and ammonia-producing bacteria might be explained by some biologic activity as yet not understood. Perhaps groups of individual bacteria create an acidic micro-environment while catalyzing the ammonia-producing reaction. Precipitation of newberyite spherules might begin in such a micro-environment.

### *Hannayite*

Noted five times in this series of calculi, hannayite,  $\text{Mg}_3(\text{NH}_4)_2\text{H}_4(\text{PO}_4)_4 \cdot 8\text{H}_2\text{O}$ , is a triclinic mineral occurring as soft, white, sheaf-like laths and radial sprays. In four cases it encrusts calculi in loose crystalline aggregates; in the fifth it constitutes denser, probably initial deposits of intergrown sheafs radiating from many centers. Associated minerals are apatite and struvite (3 cases); apatite, struvite, and newberyite (1 case); and apatite, whewellite, and weddellite (1 case). The formula and varied association of hannayite suggest that it represents a response to near-neutral conditions in the urinary system. Molecular ratios with respect to magnesium indicate that slightly acidic conditions would be favored. Its rarity is probably caused by the difficulty of maintaining a delicate pH balance in the human body over significant lengths of time.

### Miscellaneous Urinary Minerals

Early chemical analyses of calculi frequently reported calcium carbonate as a stone constituent; this error resulted from the presence of carbonate in the apatite structure. Beck and Bender (1969) described the first *bona fide* calcium carbonate urinary calculi, which included both calcite and aragonite. In the present study, calcite was found four times, always as yellow to brown, granular, poorly consolidated material not associated with other minerals.

Two calculi composed of weddellite crystals deposited on globular whewellite contained as a last deposit colorless cubic crystals of halite. Calculi which are stored in saline solutions sometimes are encrusted after drying with a thin crust or scattered powdery halite, but in the two cases observed the crystals were about  $1\frac{1}{2}$  mm in size, and were intimately intergrown with the angular weddellite crystals. No speculation as to the genesis of halite in the human body is offered at this time.

Finally, two sulfates were identified in calculi. Gypsum,  $\text{CaSO}_4 \cdot 2\text{H}_2\text{O}$ , occurred three times, always as fragile, colorless monoclinic crystals about 0.3 mm long, on surfaces of calcium oxalate stones.

Hexahydrate,  $\text{MgSO}_4 \cdot 6\text{H}_2\text{O}$ , was identified in one calculus containing newberyite, apatite, struvite, and  $\text{Mg}_3(\text{PO}_4)_2 \cdot 4\text{H}_2\text{O}$ . Hexahydrate can crystallize metastably in contact with solution at human body temperatures, but epsomite,  $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$ , is the stable phase. It is possible that the few poorly-bladed to granular hexahydrate crystals in the stone dehydrated from epsomite after removal from the body.

### Non-urinary Pathological Minerals

Gall stones usually consist of organic compounds such as cholesterol, but stones composed entirely or in part of three calcium carbonate polymorphs (calcite, aragonite, and vaterite) have been observed. As mentioned above, prostatic calculi are almost always whitlockite; some apatite may be associated. About 50 salivary gland stones analyzed in this study were all pure, dense, porcelainous, white-to-yellow apatite; a single tonsil stone was powdery white apatite; and a single pancreas calculus was calcite. The few calculi observed from the liver and from joint deposits were all organic compounds.

### Pathological Significance

Minerals in calculi are usually grouped according to their cations or anions or both. However, in the following discussion of pathology the writer suggests two possible broad categories not based on major-element chemistry: precipitates whose crystallization is known or suspected to be directly influenced by minor elements or infective organisms (catalyzed precipitates), and those lacking such influences (simple precipitates). In addition to this speculation regarding initial precipitation, purely observational paragenetic data is incorporated.

#### *Catalyzed Precipitates*

As discussed above, whitlockite precipitation is known to be affected by small amounts of Mg and Zn. Microprobe work in progress will hopefully uncover the structural role of these elements, as well as providing quantitative information on amounts involved.

The magnesium phosphates all show evidence for origins closely related to the infections with which they are associated. Newberyite spherules are found scattered abundantly on stones' surfaces, and hanayite laths radiate from many centers. This strongly suggests that individual crystalline aggregates may be deposited initially upon small concentrations of the infective organism. Large complex molecules are

another possible source for the necessary multitude of nuclei, but organisms are known to be present and provide the simplest explanation. In the case of struvite, the large number of single crystals in a stone may also reflect nucleation upon many centers composed of single organisms or small groups. (Based on actual cross-sectional crystal counts, over 7000 individual struvite crystals occur in a typical small ( $4 \times 1\frac{1}{2} \times 1$  cm) apatite-struvite staghorn calculus.) Struvite is almost invariably associated with apatite; perhaps the magnesium phosphate is stabilized or its precipitation catalyzed by the infective organism, as suggested above for newberyite.

#### *Simple Precipitates*

Renal papillae are small protrusions within the kidney containing small ducts which transmit urine from the kidney tissue into large collecting chambers within the kidney. Tips of papillae are the site of initial deposition for more than one-third of all calculi, most of which contain calcium oxalates, apatite, and brushite. The nucleus is invariably external to the main part of the stone, and is almost always very small with respect to the rest of the calculus. Apatite, and less commonly, brushite, build up on the surfaces of papillae or within their ducts. Some urologists believe that small amounts of calcium phosphate at that location are normal. Nonetheless, these apatite and brushite buildups serve as the nuclei for many if not most papillary calculi. (Small external nuclei of apatite and brushite are fragile, and may break away from a stone before analysis.) Subsequently, whewellite in concentric laminations is usually deposited, followed by dipyrnidal weddellite crystals. More apatite may deposit at any time, especially in crevices between globular whewellite bodies or interstitial to weddellite crystals. Many large brushite calculi have papillary cavities lined by apatite.

Among calculi not deposited initially on renal papillae, apatite still is found as the most common nucleus. Stones with whewellite nuclei are usually pure whewellite, but they may have weddellite crystals on their surfaces. Weddellite is rarely found in nuclei of stones.

All these "simple" precipitates are probably actually catalyzed to some extent by organic compounds, both solid and liquid, which are ubiquitous in the urinary system. In addition to the known role of organic material as a pigmenting agent, and its suspected influence in crystallization of glassy

apatite, it may affect crystallization and precipitation in other, unsuspected ways. The presence of organic matter should never be ignored in studies of urinary minerals, although its effects are hard to evaluate.

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