Urol. Res. 9, 259-261 (1981)

Urological Research

Studies on the Morphology of Human Uric Acid Stones

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Accepted: April 7, 1981

Summary. Human uric acid renal stones are easily distinguished from other urinary calculi by their globular or spherical shape, their colour and their hardness. Investigations of uric acid crystals grown in the presence of a variety of pigments indicate that a disordered layer structure of the uric acid dihydrate is responsible for the colour of such crystals, caused by the inclusion of pigment molecules into the crystal lattice. This in turn may help to explain the other special properties of uric acid stones.

Key words: Uric acid crystals, Pigments, Renal stones.

INTRODUCTION

Uric acid stones growing in human urine exhibit several characteristic and unique properties.

Firstly, in marked contrast to all other renal calculi (with the possible exception of calcium carbonate, only a minor component of calculi) uric acid stones are often of a brick-red or orange-grey colour.

Secondly, independent of the final outer form, the inner core is almost always globular. Often the entire calculus adopts a spherical form with concentric layers surrounding the inner core (Figs. 1-3).

Thirdly, uric acid stones are the among hardest in human urinary lithiasis.

In this paper we attempt to relate these properties to the nature of crystalline uric acid and the way in which pigments responsible for the colour are incorporated. The study concentrated on uric acid crystals grown in the laboratory in the presence of a variety of staining pigments.

MATERIAL and METHODS

Stained crystals of uric acid were grown by a technique described in detail elsewhere (1, 2). In principle water soluble sodium urate with added pigment was acidified, resulting in uric acid crystals. Alternatively, pure uric acid was dissolved in boiling water and slowly cooled down. The pigment was added at about 65-70°C and crystallisation initiated by immersion of a piece of twine. Pigments used in these experiments were betanin (kindly provided by Prof. A. Dreiding, University of Zürich, Switzerland), the pigments of red wine, of certain cactus plants and of roasted coffee beans, urorosein (an indol derivative), urobilin, stercobilin (kindly provided by

Fig. 1. Typical uric acid stone with globular core

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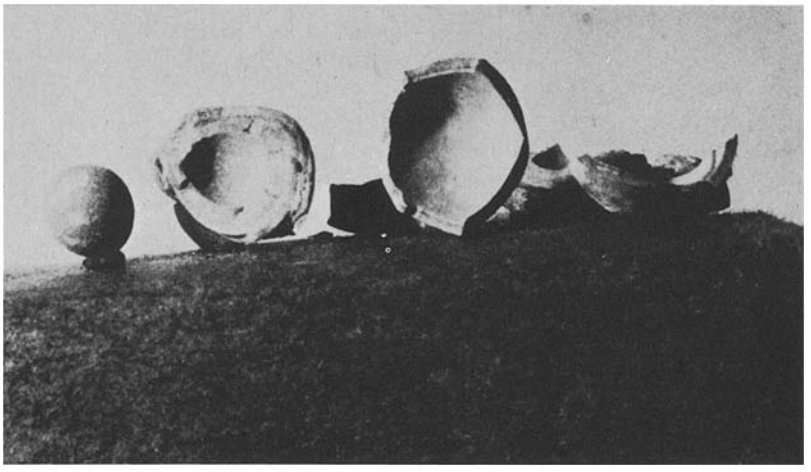

Fig. 2. Core and shells of a uric acid stone (x 4)

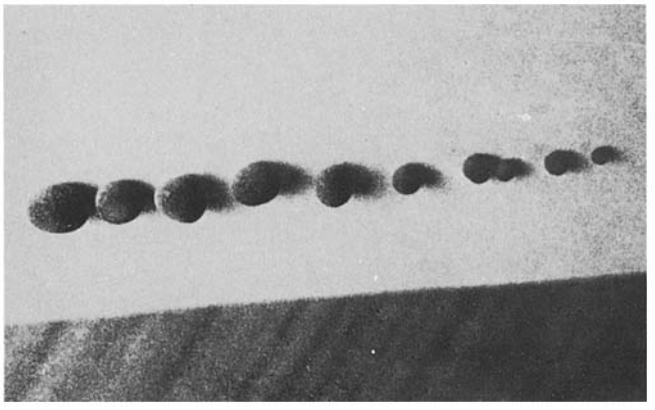

Fig. 3. A series of globular uric acid stones (all of one patient)

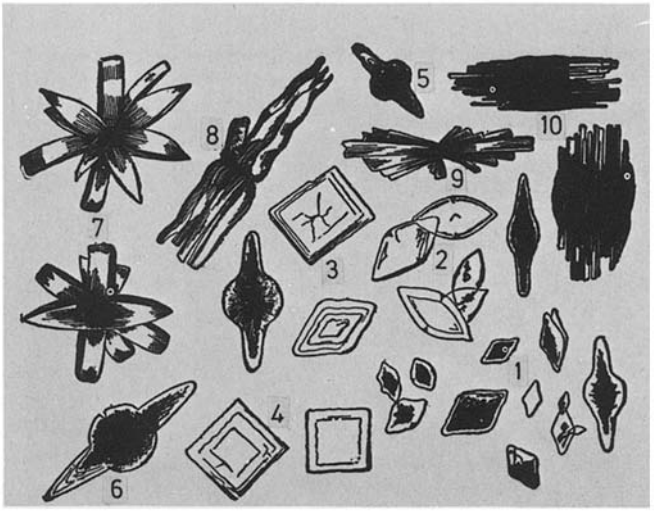

Fig. 4. 1 Rhombic plates; 2 whetstone forms; 3, 4 quadrate forms; 5, 6 prolonged into points; 7, 9 rosettes; 8 pointed bundles; 10 barrel forms precipitated by adding hydrochloric acid to urine by courtesy of McGraw Hill Book Comp. (see ref. 5)

Prof. C. J. Watson, Minneapolis, USA) and methylene blue. Single crystals for X-ray diffraction analysis were selected from these preparations. Photographs using CuK_α radiation were taken of several samples and the unit cell parameters determined.

RESULTS

The stained crystals obtained by the methods described above came in a variety of forms Often the crystals formed large clusters. In general stained crystals were somewhat larger than unstained ones grown under similar conditions.

The crystallographic investigation showed that all specimens, whether stained or not, belonged to the orthorhombic crystal class and had identical cell dimensions of a = 17.6, b = 7.4 and c = 6.4 Å. The diffraction patterns, however, showed variations of intensities and extinctions from crystal to crystal, even if taken from the same crystallisation batch. Such behaviour is typical for disordered crystals and in general prevents assignment of a unique space group and a detailed three-dimensional structure analysis.

DISCUSSION

Uric acid exists in three different crystal forms (8). Anhydrous uric acid crystallises in two monoclinic forms, A(I) with a unit cell of a = 13.12, b = 7.4, c = 6.20 Å, $\beta = 90.5^\circ$ and A(II) with a = 13.02, b = 7.59, c = 6.18 Å, $\beta = 93.1^\circ$.

The complete three-dimensional structure of A(I) has been established by X-ray analysis (8). Modification A(II) is believed to be an intermediate in the formation of the anhydrous form A(I) from the dihydrate, form B, which has an orthorhombic unit cell, a = 17.55, b = 7.40, c = 6.35 Å. The diffraction pattern of dihydrate crystals shows variations of intensities and extinctions. The stained crystals grown in our experiments also belong to this form B, with the same unit cell dimensions and the same characteristic diffraction pattern variations.

It has been known for some time that both anhydrous and hydrated uric occur in urinary calculi. In a survey conducted by Ringertz (8), about half of the calculi investigated consisted of form A(I) and the other half were mixtures of A(I) and B. Interestingly, the biological uric acid dihydrate is more stable than the synthetically produced product, which loses water quite easily, Hydrated uric acid of form B was found in urinary calculi stored in air for 200 years (4, 9). It was assumed (3) that pigments of biological origin were responsible for the staining and the increased stability. The stained crystals made in our experiments also proved to be very stable. We were not able to detect any alteration of crystal quality over a period of two years.

On the basis of these facts and our findings we propose the following hypothesis to explain the staining of uric acid calculi as well as of laboratory-grown crystals and their stability.

Dihydrated uric acid seems to form a rather loose-layered structure, interconnected by a network of hydrogen bonds. These layers contain random gaps and misfits (witnessed by the variations of the diffraction pattern) which tend to destabilise the crystals. By losing water the crystal changes to the more stable anhydrous form. Addition of certain pigments - artificial in our experiments, or of biological origin in calculi - seems to fill some of the gaps and thus to stabilise the crystals. In this process the unit cell dimensions do not change. Note also that all the stains and pigments used in our experiments are molecules with at least a substantial planar part, thus fitting well into a layer network. The stabilising effect of stains and pigments is also supported by our observation that stained crystals are generally larger than unstained ones and easily form aggregates (1, 2). Crystal aggregates enhance stone formation.

Furthermore, a study (3) showed that only stained uric acid crystals (naturally or artificially stained) can be pressed into tablets. This fact proves, in our opinion, that (some) urinary pigments possess stickiness. It has also been found (6) that patients with uric acid stones excrete more of this peculiar stone pigment than healthy people. And still another property of several urinary stains, such as indol or pyrrol derivatives must be mentioned in connection with urinary stone formation; they are mostly polymers with a tendendy of further polymerisation, thus contributing to the solidification and hardening of uric acid calculi.

The formation of a globular core in these stones may have its main cause in the (relative) plasticity of uric acid crystals with their loose layer structure, random gaps and misfits. Such imperfect and deformed crystals possess plasticity (10). If aggregates of pigmented "plastic" uric acid crystals are rolling in the renal calices, they may be moulded to globular shape. By partial or total dehydration, by polymerisation and solidification of the pigments, the small stone will gradually get harder. Further layers of the same material adding to the stone's growth will undergo the same process. The end-product is a pigmented elliptical or globular hard stone.

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