Spherulites of Calcium Oxalate in Uroliths: Morphology and Formation Conditions

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Among the mineral phases composing human uroliths, the most widespread are spherulite aggregates of calcium oxalate monohydrate ($CaC_2O_4 \cdot H_2O$). The morphology of these aggregates and their formation conditions have been studied. They are regular products of crystallization under the conditions of high supersaturation existing in the kidney. Formation of $CaC_2O_4 \cdot H_2O$ crystals takes place mainly by means of heterogeneous nucleation, and their growth goes in kinetic regime. Destruction of oxalate concrements by means of distance shock-wave lithotrypsy (DSWL) creates many problems to medical men and patients due to anatomic peculiarity of the spherulite aggregates. In these, nuclei of two types – calcium phosphates + organic matrix, or $CaC_2O_4 \cdot H_2O$ microcrystallites – are distinguished. Subindividuals in an aggregate have a fine-fibered structure complicated by helicoidal torsion, which accounts for their abnormal strength characteristics and makes one recognize that the distance destruction by means of high-energy impulses is the least expedient method of their disintegration and removal from the organism.

INTRODUCTION

At present, urinary calculosis (UC), or urolithiasis, occupies one of the leading places among urological diseases and affects people of the most efficient age – of 20 to 50 years old [1]. Irrespective of the method of removal of uroliths, it is associated with heavy complications and a strong tendency to relapses, which results in frequent and long-term loss of working capacity. Out of every 1000 persons suffering from urolithiasis, 18 become permanently disabled [2–4]. The frequency of this pathology in human population is progressively increasing, which gives the reasons to consider it as a "civilization disease" [5].

The distance shock-wave lithotrypsy (DSWL) method introduced into the clinical practice in the 80's of the **XX** century has radically changed the tactics of urolithiasis treatment and occupied the leading place in it [6]. At the same time, despite its effectiveness and slight invasiveness, DSWL fails to solve the urolithiasis problem on the whole. The current possibilities of lithotrypsy not so much result in recovery from the disease as increase the number of patients with chronification of the pathology [7].

In developed countries, 90 % of cases of urolithiasis are determined by concrements in kidneys and ureters composed of calcium oxalates [8] which are less destructible by shockwaves as compared to other uroliths and during elimination of fragments traumatize more strongly the ureter mucosa [9–11]. Crystallomorphological analysis of uroliths composed of $CaC_2O_4 \cdot H_2O$ permits explaining the specificity of their behaviour in lithotrypsy proceeding from the peculiarities of structure of the spherulite aggregates formed by them, and

may turn out to become a source of valuable information about the mechanism of urolith formation. Since the morphology of mineral individuals and of their aggregates is largely determined by the mineral-forming medium, one can solve, by the form and structure peculiarities of urolith, "inverse problems", *i. e.* reconstruct the conditions of their origination and the kinetic peculiarities of growth processes.

In the present work, spherulites of calcium oxalate monohydrate composing uroliths were studied, since it is just they that behave in the most problematic manner in DSWL. Spherulite forms are widespread in the mineral world. At present, the conditions of their formation and growth have been well studied [12−15], which makes it possible to use the body of mineralogical data for the interpretation of the mechanisms of oxalate urolithiasis.

EXPERIMENTAL

Uroliths of 240 patients with UC at the age of 18 to 76 years old (96 males and 144 females) were studied. For removal of concrements, 126 surgical operations and 107 DSWL seances on a lithotryptor Direx XI (Israel) were carried out. In 12 cases, stones came out by themselves. The proportion of proper oxalate concrements in the sample studied made up 25 % (61 specimens); another 33 % (80 specimens) contained $CaC_2O_4 \cdot H_2O$ as a accompanying phase.

A comprehensive study of the phase composition of uroliths was carried out at analytical laboratories of the United Institute of Geology, Geophysics and Mineralogy, SB RAS. Qualitative X-ray analysis was used for identification of crystalline phases whose content
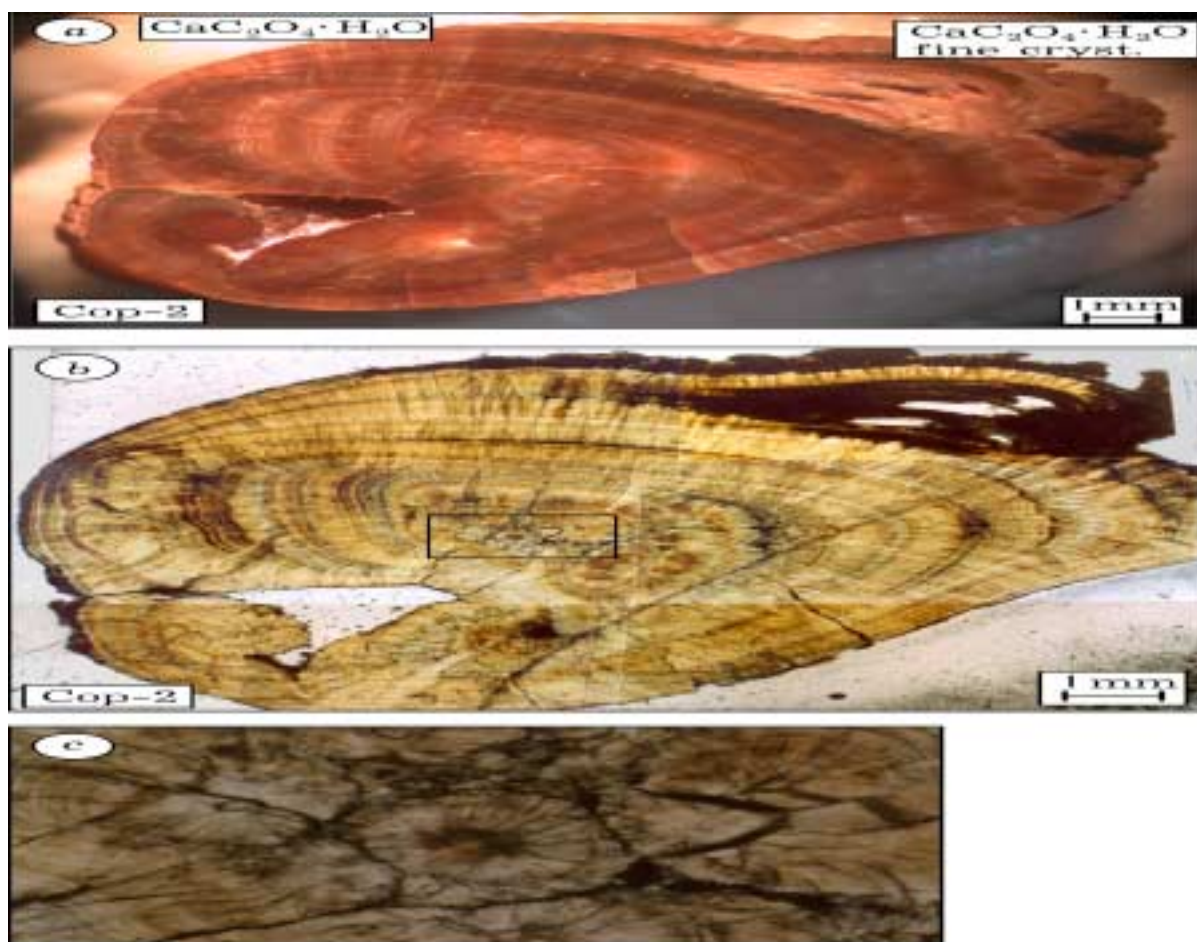

Fig. 1. Appearance (*a*) and inner structure (*b−d*) of typical $CaC_2O_4 \cdot H_2O$ spherulite stones: *a* − chalcedony-like stone composed of numerous small spherulites; *b, c* − stones representing a concentric spherulite (*b* − polished section cutting the central part of the stone, *c* − petrographic thin plate (polarized light, nicols X)); *d* − a magnified fragment of *c*: an apatite nucleus overgrown by a $CaC_2O_4 \cdot H_2O$ spherulite aggregate (polarized light).
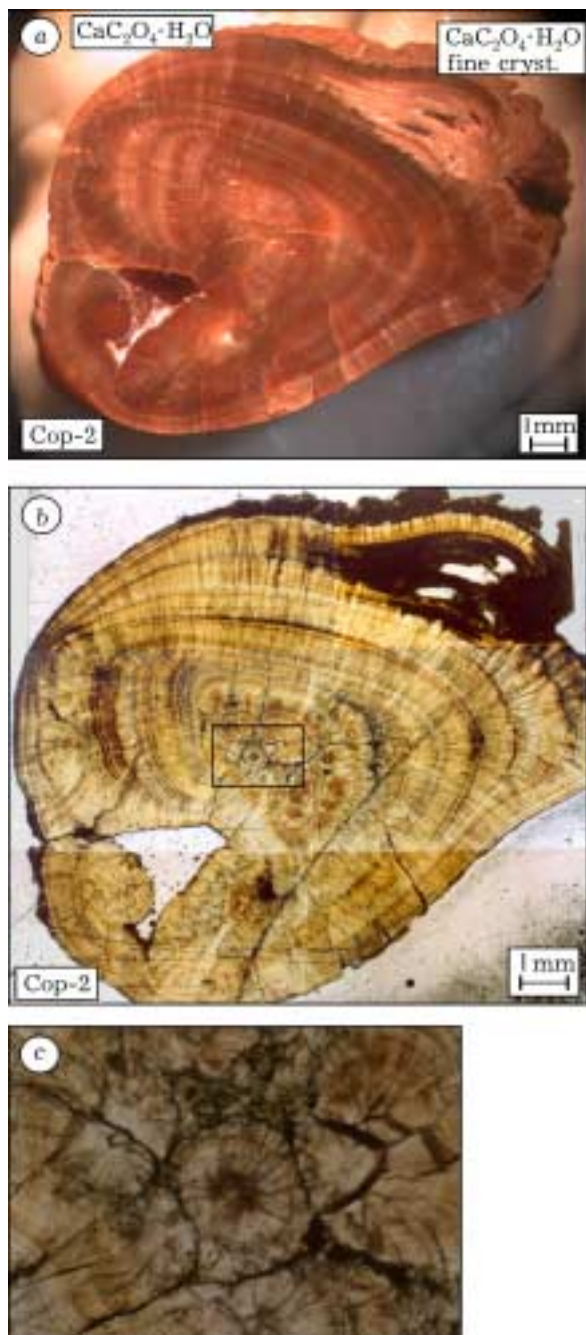
Fig. 2. Inner structure of a polycentric spherulite $CaC_2O \cdot H_2O$ urolith with a separate "pocket" of fine-crystalline $CaC_2O_4 \cdot H_2O$ in the external zone: a − polished section (common light); b − petrographic thin section; light zones of pure $CaC_2O_4 \cdot H_2O$ and dark zones enriched with organic substance are clearly visible; black is an aggregate of fine-crystalline $CaC_2O_4 \cdot H_2O$ (polarized light); c − a magnified fragment of b; numerous $CaC_2O_4 \cdot H_2O$ microspherulites composing the nucleus of a large stone; in the centre of spherulites, no phases but $CaC_2O_4 \cdot H_2O$ have been detected (a petrographic thin section, polarized light).

exceeded 5 %. The works were carried out according to the standard technique [16] on a diffractometer DRON-3 (CuK_α radiation, $U = 30 − 40$ kV, $I = 30$ μA). Phase identification was performed by comparing with standards of the "Roentgenometric Catalogue" [17] and of its computerized analogue − the software packet DXRWin 2.0. The scanning electron microscopy (microscope JSM-35) as the basic method of crystallomorphological analysis permits making phase diagnostics and determining their temporal relations. The objects were photographed on gold spray-coated preparations, the qualitative chemical composition was estimated on carbon spray-coated preparations. Photography of objects at small magnifications (up to 30) was performed by means of a digital camera and a binocular microscope MBS-2. Optical observation of phase relationship and evaluation of the phases' quantitative proportions were carried out on a polarization microscope POLAM-P-211.

SPHERULITES' STRUCTURE AND FORMATION CONDITIONS

In the simplest case, a spherulite is the form of crystal adapted in the best manner to nonequilibrium growth conditions. At the expense of its crystalline homogeneity, the individual, in accordance with the Curie principle, acquires a spherical or a hemispherical symmetry, conforming with the symmetry of the crystallization medium [13]. Formation of spherulites is promoted by a high supersaturation and the high crystal growth rate determined by it; by capture of mechanical and structural admixture; by a high viscosity of the crystallization medium, low growth temperature; combined crystallization of several phases; alternation of growth and dissolving periods [12, 13]. In the spherulite structure several zones can be detached. The nucleus may be represented by any estrange fragment which plays the role of the seed crystal. In this case, the spherulite can first be formed as a polycrystalline aggregate [14] of several split individuals (Figs. 1, 2). In some cases, its growth begins from a monocrystalline nucleus of a
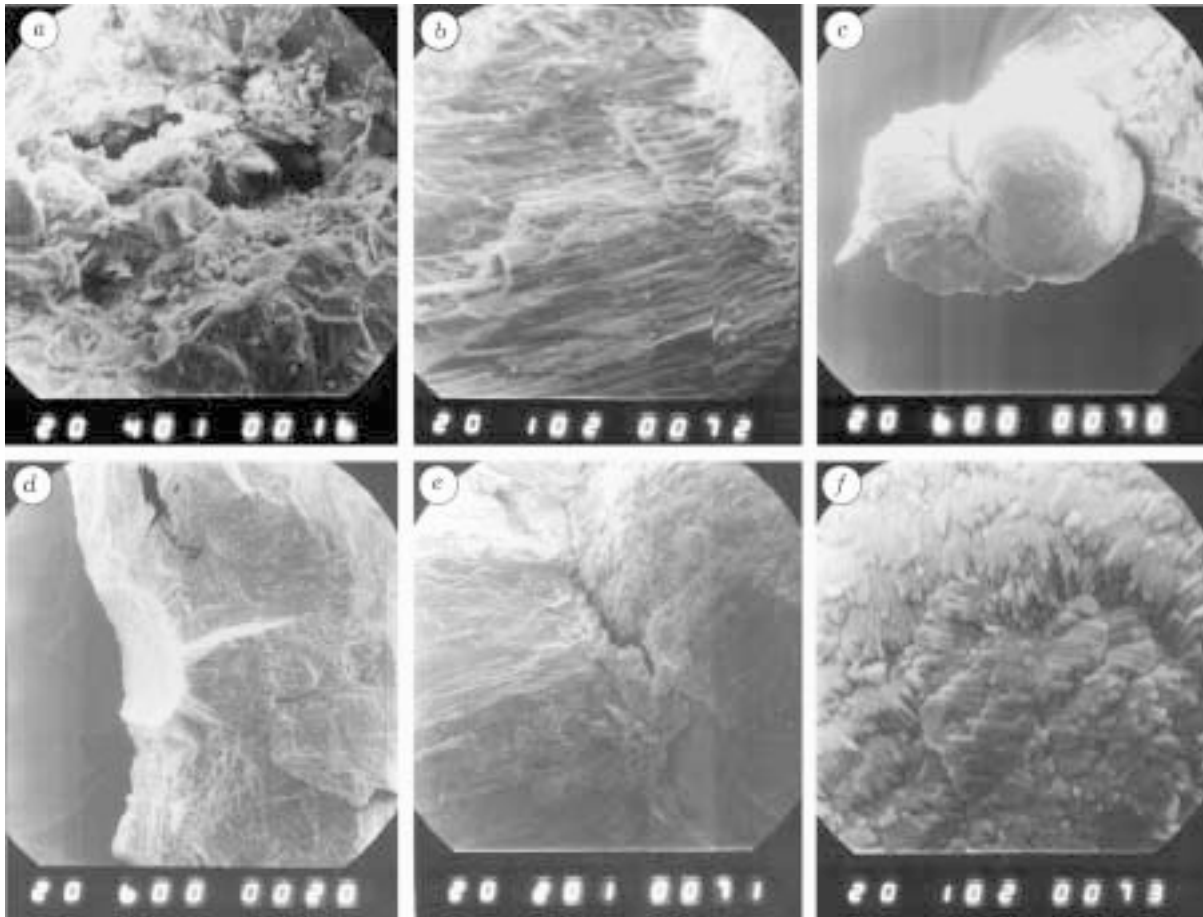
Fig. 3. Inner anatomy of $CaC_2O_4 \cdot H_2O$ spherulite stones (Sp. Su-1): a − microcavities in the central part (×400); b − structure of an aggregate of subparallel thin-columnar individuals; there are no cavities (×1000); c − a $CaC_2O_4 \cdot H_2O$ microglobule in the centre of a spherulite zone; a destroyed fragment of a monophasic $CaC_2O_4 \cdot H_2O$ concrement (×60); d − a "mould" of a globule in the base of the next growth rhythm in a concentrically zonal stone (×60); e − a crack on the border of junction of two large growth rhythms in a spherulite stone (×200); f − block surface of a globule formed by well-developed heads of needle-like microindividuals.

microscopic size; then the spherulite represents a product of splitting of one crystal (spherocrystal). Primarily, subindividuals have a conical form, however, as the splitting intensity grows, they begin to interact with each other, following the law of geometrical selection. Optimally oriented individuals whose elongation coincides with the radius of the future spherulite are subsequently transformed into finest fibres, often helically twisted like yarn (see Figs. 1, b, c; 2, a, b; 3, b).

SPHERULITE $CaC_2O_4 \cdot H_2O$ AGGREGATES

By their appearance and internal anatomy, spherulites of monohydrate calcium oxalate are similar to typical representatives of this morphological class − chalcedonies or agates.

They have a clear-cut rhythmical structure: a more or less clear nucleus, a zone of geometric selection, a thin-columnar aggregate, edged subindividual heads. The microrhythms are visually distinguishable by the irregular pigment distribution. The presence of irrization effect in $CaC_2O_4 \cdot H_2O$ spherulites permits asserting that as many as several hundreds microrhythms can be contained in 1 mm.

The nucleus of oxalate concrements is often composed of extraneous finely dispersed material (see Fig. 1, d) or contains a cavity (Fig. 3, a). The central part of uroliths of this type is, as a rule, filled up by amorphous phosphates or by globular biogenic apatite in a complex with an organic matrix [18−24]. The main cause of the constant coexistence of these phases is most probably the structural similarity

between the apatite and DNA molecules which makes possible their epitaxial relations [25, 26]. In the centre of early nascent spherulites the organic matrix is not always conserved, whereas at the base of late small spherulites decorating the concrement surface, blood clots have often been found, which directly witnesses to the possibility of oxalates sedimentation on an organic matrix.

More seldom, one fails to detect a clear-cut nucleus in $CaC_2O_4 \cdot H_2O$ spherulites (see Fig. 2). In this case, they may be regarded as a normal product of crystallization on their own intensely split seed crystal. The data of [27] on the morphology of $CaC_2O_4 \cdot H_2O$ microcrystallites ($3-10$ μm) excreted in crystalluria (Fig. 4) witness to the fact that all of them are split individuals whose expansion must inevitably result in a spherulite formation [13].

The size of coarse-columnar $CaC_2O_4 \cdot H_2O$ individuals is about 2 μm, which is typical of spherulite-like formations. Individuals in an aggregate are adjusted to each other very tightly, without any commensurable cavities between them (see Fig. 3, b, $d-f$). This accounts for the maximal density of concrements of this class as compared to the porous uroliths of other chemical and phase composition. Polarized light makes it possible to see the thin-fibre structure of individuals which are not extinguished at any position of nicols, witnessing to torsion of the fibres that compose them (see Fig. 1, c). A similar observation was made earlier [18, 23].

In mechanical destruction of spherulites (see Fig. 3, c, d) the surfaces of internal zones often representing aggregates well-developed micro-individual heads (see Fig. 3, f) turned out to be opened. It permits asserting that in the process of spherulite formation there were time intervals sufficient for edging the individuals that had at one time gone out into the free volume
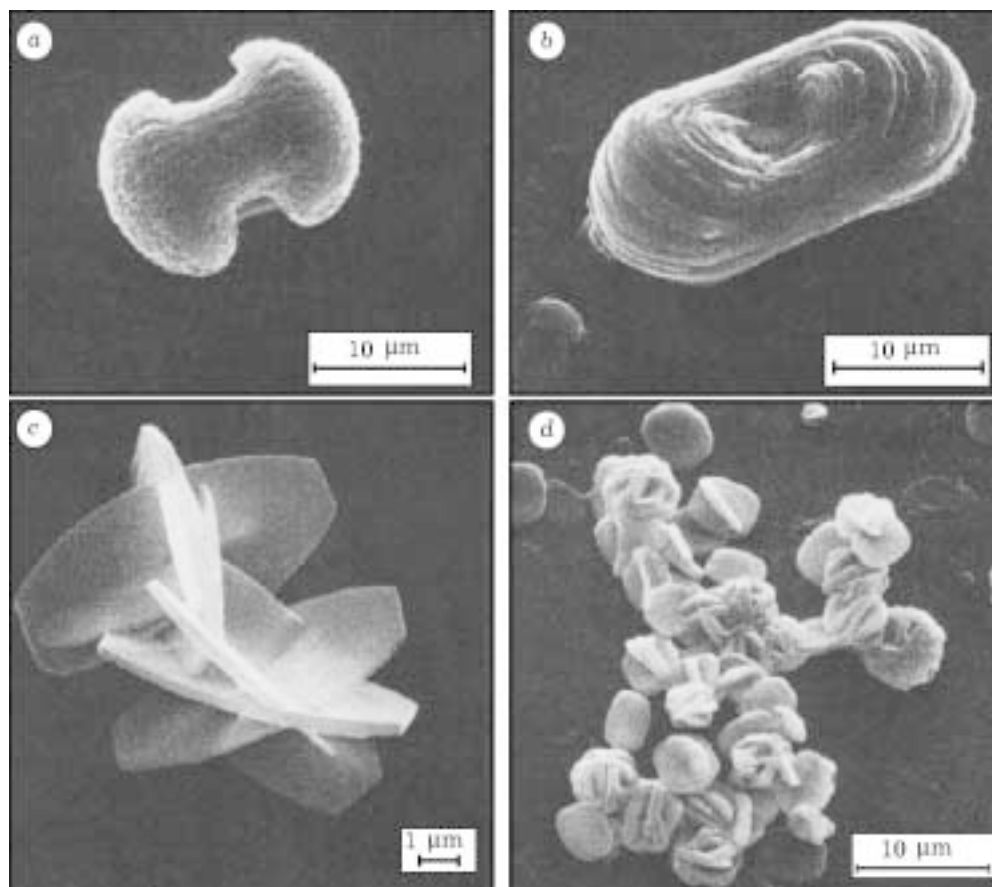

Fig. 4. Typical appearance of $CaC_2O_4 \cdot H_2O$ microcrystals (a, b) and their aggregates (c, d): a − a desmine-like split crystal; b −a hooper-like crystal; c, d − $CaC_2O_4 \cdot H_2O$ "roses" (electron photomicrographs of crystalluria products, according to P. G. Werness *et al.*, 1981).

of the nutrient medium. The increase in subsequent zones went on the primary spherulite as the seed crystal. In shock destruction of spherulite aggregates, it is just on these surfaces that exfoliation takes place most easily.

KIDNEY AS A GROWTH SYSTEM

Urine is not an ionic, but a colloidal, solution capable of existing without crystallization phenomena at a 2−3-fold excess of concentration of respective components over the product of solubility of the main concrement-forming phases − oxalates, phosphates and urates. Retention of cations and anions in a dissolved state by means of their transition from ionic forms to complex compounds is the basis of the mechanism of inhibition of growth of mineral phases in the urine system. Most frequently, inhibitors of stone formation are citrate, pyrophosphate ion, some proteins and magnesium [24, 28].

Real forms of existence of Ca^{2+}, Mg^{2+}, $C_2O_4^{2-}$, , *etc.* in urine are often unknown. That is why the knowledge of their absolute concentration does not permit predicting unequivocally the potential possibility of formation of uroliths in the organism of a concrete patient. In the first approximation, a satisfactory clinical prognosis can be obtained by going to the level of estimation of cation and anion activity taking into account the ionic strength and pH of the solutions. The degree of reliability of the forecast increases when using a software packet which makes it possible to estimate quantitatively the contribution of soluble complex compounds and ionic pairs to the total balance of Ca^{2+}, Mg^{2+}, Na^+, K^+, , , , $C_5H_4N_4O_3$ *etc.* in the patients' urine [24]. However, an important role in the concrement formation is played not only by thermodynamic, but also by kinetic factors. A comprehensive consideration of mutual influence of the solution supersaturation degree, the presence of inhibitors hindering the formation and aggregation of microcrystallites, the character of the organic matrix, epitaxy phenomena, as well as the position in which the nucleation and growth of the urolith took place [20, 24, 27].

For any mineral individual to be formed, the stage of germ formation is of primary importance. Nucleation is subdivided into homogeneous (spontaneous) and heterogeneous one which takes place on the phase separation surface or on extraneous particles playing the role of seeds. The homogeneous nucleation process is practically always complicated in comparison with the heterogeneous one, due to which homogeneous saturated solutions are capable of existing rather long without crystallization. The time necessary for a microindividual to reach the critical size and begin crystallization is referred to as induction period [13, 29].

The growth of mineral phases in such a "crystallizer" as kidney will be determined, firstly, by the colloidal state of the solution and its high supersaturation; secondly, by the discrete character of liquid supply to the renal pelvis; thirdly, by the shortness of the renal pelvis filling and evacuation periods. The maximally possible urine excretion by the kidney is 20 ml/min, the minimal one 0.5 ml/min. On the average, the phase of filling the kidney pelvis with urine lasts 10−15 s, and the evacuation is completed in 2−3 s. The pause between evacuations is from 20 to 120 s [30]. For this reason, the most probable seems heterogeneous nucleation of mineral individuals in the kidneys, since an induction period of no more than 2 min is too short for a spontaneous formation of microcrystallites even in highly concentrated media. At present, one can distinguish seeds of at least two types.

Nuclei of a considerable part of $CaC_2O_4 \cdot H_2O$ type spherulites are composed of amorphous phosphates, globular hydroxyl- or carbonate apatite that form tight aggregates with organic matrices of various composition and nature (see Fig. 1, *c*, *d*). For the given case, the most logical appears the interpretation proposed earlier by I. S. Kolpakov [31] and V. I. Katkova [22]. Fragments of exfoliated epithelium, blood clots, bacterial colonies may have been the primary phase nonhomogeneities (seeds) in the supersaturated solution on which a mass heterogeneous nucleation and subsequent crystallization of phosphate microindividuals (organic phosphate nuclei) or a direct settling of oxalates ("old" spherulites with cavities instead of nucleus or

"young" spherulites with conserved non-min-eralized organic matrix at the base) took place.

Seeds of the second type may be the centre of formation of spherulites "without nuclei" [20, 31]. In this case, the most probable is spherulite formation on a split seed crystal of the same kind (see Fig. 2, c). Electron micrographs of split $CaC_2O_4 \cdot H_2O$ microcrystallites − crystalluria products [27] confirm convincingly the possibility of realization of such a variant (see Fig. 4).

Besides, the author of [24] proposed a hy-pothesis of calcium oxalate crystallization on microseeds of uric acid and its salts. It was based on indirect indicators, such as the high correlation between hyperuricoseuria and oxalate concrement formation. We have ob-tained direct mineralogical confirmations.

NUCLEATION PHENOMENA IN KIDNEYS

Theoretically, generation of crystallites is possible in any part of the urinary system. Therein, the highest degree of contrast has to be demonstrated under nucleation conditions in the urinary bladder and in the very kid-neys. The authors of [27] hypothesize that the majority of microindividuals excreted with urine in crystalluria are products of homoge-neous nucleation and direct crystallization from the colloidal solution. However, homogeneous nucleation requires a considerably long induc-tion period and is therefore possible only un-der relatively stable hydrodynamic conditions which are not met by the kidney. Diastolae, systolae and pauses after them amount to 14 s for renal calyces and 32 s for renal pelvis. For this reason, the authors of [27] reject the kid-ney as the organ that generates the major part of crystalluria products and tell in favour of their crystallization in the urinary bladder. From the point of view of the crystal growth theory, this hypothesis is absolutely logical.

Crystalline germs that act as nuclei of kidney concrements can be produced only directly by the kidney. Direct optical observations of kid-ney tissue slices, and the data of [18, 32−34] witness to the fact that at least one of the posi-tions of generation of crystalline microindivid-uals are kidney cortex canalicules (Fig. 5, *a, b*). Primary microlite, mostly attached to the canali-
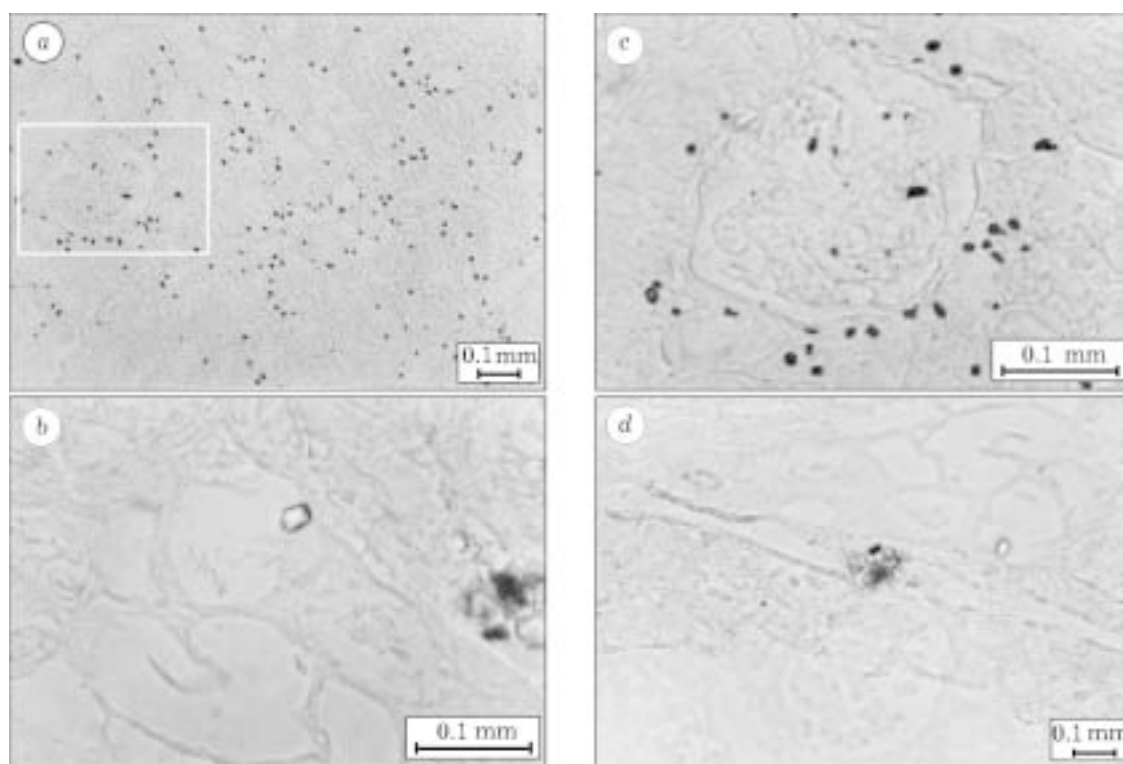

Fig. 5. Sections of kidney tissue demonstrating the microlite distribution pattern (polarized light): *a, b* − the least microlites of unidentified phase; *b* − a magnified fragment of *a*; *c* − a single uric acid crystal attached to the canalicule wall and containing several black microlites; *d* − an aggregation of uric acid crystals obtruding the canalicule.

Fig. 6. Asymmetrical $CaC_2O_4 \cdot H_2O$ spherulite stones demonstrating typical hollows with interruptions of growth layers − possible sites of attachment of stones to kidney tissues.

be detained and form aggregates (see Fig. 5, *d*). The mechanism of their aggregation and of subsequent participation in stone formation in the general form is described by the theory of Randall − Carr [32−34]. It is noteworthy that, *caeteribus paribus,* both the generation and the attachment of microlites are facilitated when inflammatory processes develop in the kidney and the integrity of epithelial covers is disturbed [18, 24].

Another factor which has to be considered as being of paramount importance for the uroliths formation, is the possibility of detaining the seed crystals and its attachment to soft tissues. It is obvious that elimination of microcrystals or organic associates from the urinary tract with the urine flow makes expansion of the concrement impossible. The theory of "attached particle" proposed in [24, 35] based on taking into account the urine movement speed, the degree of its supersaturation and the anatomical peculiarities of the kidney ascertains an extremely small probability of formation of freely moving stones primarily deprived of attachment sites in the kidney.

Ontogenetic analysis of small size (3−7 mm in diameter) and mass (about 0.5 g) oxalate concrements has permitted us to find among them stones having reliable sites of attachment to the substrate (Fig. 6). These sites can be distinguished on the stone surface as hollows with a characteristic sculpture of breakage of growth layers of mineral aggregates in the places where they had contact with soft tissues.

BEHAVIOUR OF $CaC_2O_4 \cdot H_2O$ SPHERULITES IN DESTRUCTION

One has to recognize as wrong the assertion widespread in medical literature that "porous stones are softer than dense ones" and that "hard stones are more difficult to destroy than soft ones". In this case, a confusion of meanings of "hard" and "strong" takes place. One has to speak, no doubt, not about the hardness of minerals composing the concrements, but about the mechanical strength of the aggregates formed by them. It is generally known that it is just phosphates having the maximal hardness (up to 5 conventional units by the
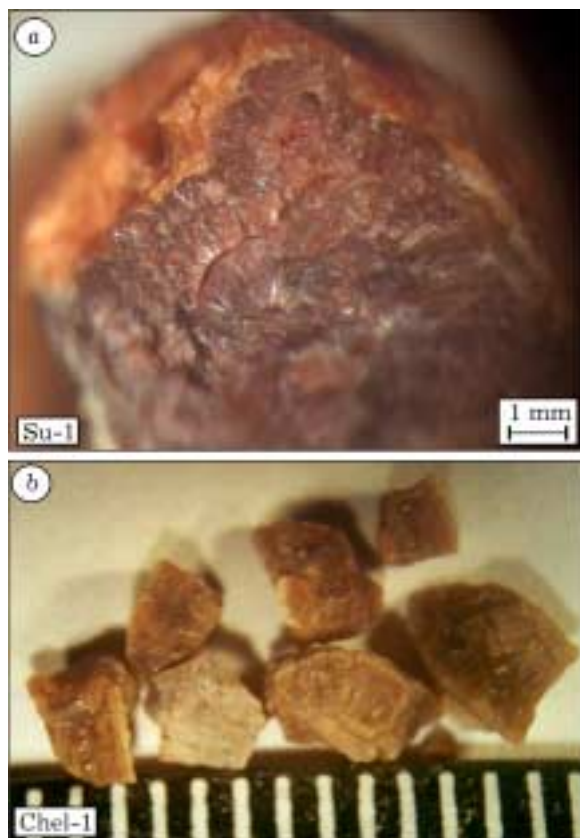
cule walls, show a weak anisotropy in polarized light. However, their small size (1 μm) does not so far allow estimating exactly their phase composition. The most probable mechanism of their origin has to be assumed the heterogeneous nucleation. In many cases, these uroliths (in numbers of 1 to 20) are diagnosed inside uric acid crystals (2 μm) (see Fig. 5, *c*). This fact permits concluding that the growth of uric acid individuals in canalicules was used mainly for seeds.

With the urine flow, the newly formed crystals move along the canalicules where they may

Fig. 7. Chip of a $CaC_2O_4 \cdot H_2O$ spherulite stone (*a*) (cracks on the borders of growth rhythms and at spherulites junctions are clearly seen) and the outer appearance of fragments of such a stone destroyed by means of DSWL (*b*).

Fig. 8. Inner structure of typical uroliths of complex composition containing $CaC_2O_4 \cdot H_2O$ spherulites in cores.

Moose scale in apatites) that form uroliths with the lowest strength characteristics and, equally to porous uric acid aggregates, are the most easily destroyed by means of DSWL. The cause thereof is the microglobular structure of uroliths of this type. On the contrary, the $CaC_2O_4 \cdot H_2O$ spherulites whose hardness does not exceed 3 (by the Moos scale) possess abnormally high strength characteristics that are determined by their fine-fibre structure complicated with the fibre torsion.

The borders between subindividuals in this case are induction surfaces of joint growth. Macroporosity is absent (see Figs. 1–3). The density of spherulite concrements approaches the theoretical density of $CaC_2O_4 \cdot H_2O$. It is just the complex of these peculiarities that determines the behaviour of oxalate spherulite concrements in DSWL. In shock wave treatment, the fibres are not broken transversally to elongation. Disintegration takes place mainly at con-
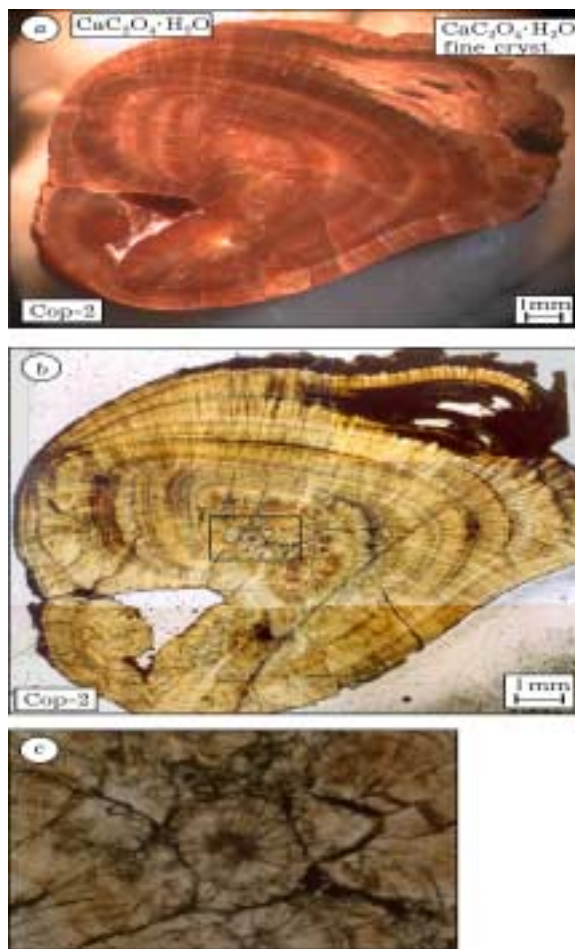
junctions of large growth rhythms (Fig. 7, *a*). That is why the fragment size is limited by the size of the pitch of uroliths' macrozonality (see Fig. 7, *b*). Destruction of spherulites along the microrhythm borders has not been noted neither by us nor by our predecessors [36]. Another "vulnerable" point of these aggregates are the borders of coupling of several spherulites; cleavage along induction surfaces of individuals' joint growth within one spherulite happens more seldom. That is why large (3–7 mm) fragments of oxalate uroliths formed during DSWL have sharp protrusions determined by the conical symmetry of spherulite segments and can traumatize soft tissues.

$CaC_2O_4 \cdot H_2O$ spherulites, like all the other spherulite formations (malachite, chalcedonies, pitchblende, brown and red "glass heads"), possess such a property as viscosity. One can easily saw and polish them, although they resist the

shock (shearing) fracture. It is just by this that the necessity of using a large number of hard, tissue-injuring ultrasound impulses in lithotrypsy of oxalate concrements is determined. Proceeding from the peculiarities of the inner structure of uroliths of this type, one has to recognize that the shock destruction is the least expedient way of their disintegration and removal from the organism. The situation is additionally complicated by the presence of spherulite nuclei composed of $CaC_2O_4 \cdot H_2O$ in concrements of complex phase composition whose external zones form uric acid or $CaC_2CO_4 \cdot H_2O$ crystals (Fig. 8). That is why of great importance becomes the development of methods of remote estimation of phase composition of the uroliths which will permit choosing the optimal method of their extraction.

CONCLUSIONS

$CaC_2O_4 \cdot H_2O$ spherulite aggregates are regular products of crystallization at high supersaturation which is always present in a kidney. Their germination takes place mainly by heterogeneous nucleation. Once formed, the concrement remains as a seed crystal throughout the time of its presence in the human organism and continues to increase its mass even at sharp changes of physicochemical conditions. Products of such processes are zonal uroliths of complex phase composition.

The composition of the spherulite nucleus playing the role of seed can be a source of information about the kind of pathology in the organism which has become the provoker of stone formation. In one case, the development of the process of lithogenesis is caused by the injure of renal parenchyma by microbial agents and formation of pathologically oriented mycellar glycoproteid complexes. Then the concrement nuclei turn out to contain a combination of phosphates and an organic component. Defects of specific adaptation and individual reactivity in the structure-functional processes under the influence of exogenous and endogenous factors leading to disturbancy in cellular cooperation and interaction, and to degradation of homeostasis can result in for-

mation of seeds of a different type. These are split $CaC_2O_4 \cdot H_2O$ microcrystals which are subsequently transformed inside the kidney into spherulites deprived of a clear-cut nucleus. Formation of oxalate stones on uric acid microseeds that have arisen directly in renal canalicules due to hyperuricosuria is not ruled out, either.

Optimal for the growth of split individuals (including spherulites) is the kinetic crystallization regime. It presupposes a regular renewal of the solution, an abundance of "construction material" for the growing phase and the absence of obstacles in the substance supply to the growing layer. Besides, the cleavage is promoted by the low crystallization temperature. From the point of view of crystal growing practice, the temperature of 36–40 °C that corresponds to the temperature of the human organism is undoubtedly low. The formation of spherulite aggregates, their oscillating microzonality, the presence of points of concrement attachment to the tissues permit considering the mechanism of formation of mature uroliths as analogous to that of cave stalactites. The growth of mineral aggregates in the latter case goes through the thin film of solution enveloping the stone and continuously changing its composition due to a regular inflow of new portions of the liquid.

The acts of spherulite nucleation may be interpreted as an exacerbation of the disease which provokes a sharp increase in concentration of mineral-forming ions and formation of new priming centres. Continuation of the macrorhythm corresponds to a stable course of the disease. The formation of edged spherulite surfaces means an interruption of formation of rhythmic zonality, *i. e.* a temporary cessation of crystallization of mineral phases.

Acknowledgements

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