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EDITORIAL

Trends in Calcium Stone Research

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The pathophysiological understanding of calcium stone disease is still poor. This is very well demonstrated by the various recommendations for stone prophylaxis.

It is not even known with any certainty whether stone formation begins in the parenchyma or in the cavity of the kidney. Histological examination reveals that medullary calcification is present in almost every kidney (3). If the overlying tissue bursts, superficial calcifications of the papilla come into contact with calyceal urine and can become renal stones although still fixed to the parenchyma in the early stages of their existence. Nephrocalcinosis therefore may explain why microscopical precursors of concretions are not washed out by the urine flow in contrast to ordinary urinary crystals.

Under the electron microscope renal calcifications already show a typical stone structure of concentric layers of calcium salts on an organic matrix. Although the matrix (contributing about 3% to the stone weight) seems to be an important factor for stone architecture, its role in the stone formation process is still obscure.

The stone matrix consists mainly of matrix substance A, which seems to derive from uromucoid, a mucoprotein excreted in urine. Now it is well known that elevated uromucoid excretion occurs in different kinds of renal disease or damage and seems by no means specific to stone formation (1).

Today, most workers agree that stone formation is a crystallization process in supersaturated urine. Measurements of urinary saturation by Robertson et al. (5) demonstrate that urine in stone patients is even more supersaturated in relation to stone forming minerals than urine from healthy controls. Supersaturation is generally caused by increased calcium excretion. This hypercalciuria may be related to intestinal hyperabsorption of calcium; to impaired tubular reabsorption or to elevated calcium mobilisation in bone. Therefore disturbances in the metabolism of vitamin-D, calcitonin or parathormone may be possible causal factors in stone development, although with available laboratory techniques hyperparathyroidism is diagnosed in only a few percent of calcium stone formers.

Sometimes the urine of healthy people also reaches quite high degrees of supersaturation but causes only harmless crystalluria. Thus further pathogenic factors must be involved in stone formation. Howard and Thomas (4) demonstrated in 1958, that the urine of healthy people inhibits in vitro crystallization of calcium phosphate and that in some stone producing patients this inhibitory activity is absent. Four years later Fleisch and Bisaz (2) isolated the first known biological crystallization inhibitor. This inhibitor impedes the precipitation of apatite in concentrations as low as 10^{-6}M and formation of calcium oxalate crystals in 10^{-5}M. Recently we were able to show that in recurrent male stone formers there is an impressive lack of urinary pyrophosphate-excretion.

However, the pyrophosphate concentrations measured are too low to explain the inhibitory activity of urine which can be demonstrated in various in vitro tests. Hence further crystallization inhibitors have to be assumed, although their chemical structure has remained unknown (6).

The precipitation of stone mineral in metastable supersaturated urine can be nucleated by minute traces of another salt. Besides nucleation and precipitation, two other crystallization processes, which also seem to be influenced by crystallization inhibitors, have aroused much interest in nephrolithiasis research, namely crystal-aggregation and epitactical growth of crystals.

Aggregation means the cohesion of single calcium oxalate or apatite crystals to aggregations of larger diameters. Epitaxis describes

the growth of a second crystal on the surface of an already existing one. Both have been intensively discussed at the recent International Meeting on Renal Lithiasis in Gainesville (January 1975).

In conclusion, stone formation may be defined as a disproportion between the excretion of stone minerals and nucleating substances on one hand and of crystallization inhibitors on the other. Perhaps these crystallization phenomena also play a role in nephrocalcinosis and other biological calcification processes.

Much work has still to be done to understand the kinetics of these processes and their clinical importance in nephrolithiasis.

Mineralogical examination of urinary stones by x-ray-diffraction and of their surfaces and sections by scanning microscopy complete the picture of stone history, which despite all the work already done remains obscure. Further progress can only be achieved by close cooperation of all specialists interested in stone disease and by collaboration of such different disciplines as urology, nephrology, endocrinology, biochemistry, pathology and mineralogy.

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