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ARTICLE

P.N. Rao

Debate: The key to stone formation is ...

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Not that long ago, the pathogenesis of stones was explained principally on the basis of formation of crystals which result from supersaturation of urine with stone-forming salts. The hypothesis had the attraction of simplicity. Furthermore, it is easy to measure the supersaturation of urine and make attempts to predict the risk of stone formation and formulate a treatment plan, be it dietary or medicinal. This theory, however, has not completely explained all the facets of stone disease and other theories have emerged in the past decade or so. In this debate three internationally renowned experts argue their own case for each of the three main concepts viz. supersaturation, macromolecules and tubular dysfunction.

Supersaturation

Dr. Kavanagh's bases his argument on the following:

- Supersaturation is the driving force that enables crystals to form, grow and aggregate and therefore is a necessary condition for stones to occur.
- If there are no crystals—there are no stones.
- Rare human stones (e.g. cystine stones) are rare because human urine is rarely supersaturated with those rare substances.
- Animals (laboratory or domestic) make stones only when their urine becomes supersaturated by dietary or other methods.

In further defence of his argument he uses the principle of Occam's Razor which states that "given two or three equally predictive theories, choose the simpler theory". However, one should also take into consideration Chatton's Anti-Razor argument which states that "if three things are not enough to verify an affirmative proposition about things, a fourth must be added". In explaining the pathogenesis of stones, should we use the razor or the anti-razor principle?

Whilst the supersaturation theory is simple and attractive, there are a few questions that need answers.

- In the examples of rare stones Dr. Kavanagh stated, the situations are extreme and the difference between those that form the stones and those that do not is great.
- In the more common type of stone viz. calcium oxalate, the differences in terms of supersaturation between stone-formers and those that do not are not that great, as seen in Fig. 4 of his article.
- As Dr. Khan argues in his paper, perhaps heterogeneous nucleation in urine which is in metastable limit is more important than urine in a supersaturated state.
- Perhaps for the above reason, some patients continue to form stones even after successful treatment of urinary abnormalities.

Renal tubular damage and cellular dysfunction

Professor Khan advances this theory based on further work that followed the landmark papers by Finlayson and Reid and Randall. They first concluded that crystals do not reside in the tubules long enough to become large enough to produce blockage. Therefore, the crystal(s) needs to be attached somewhere to produce the next process (whatever that might be) to produce a stone. Randall, many years ago, argued that stone formation starts as juxta-papillary, sub-epithelial plaque. The conclusions of Finlayson and Reid are still widely accepted and Randall's plaques have been revived in recent years and are gaining wide support.

Dr. Khan's arguments are:

P.N. Rao
Consultant Urological Surgeon, South Manchester University Hospitals NHS Trust, Manchester, UK
E-mail: nagaraja.rao@ntlworld.com

- Stones can only form on a nidus.
- Hyperoxaluria and crystals themselves may produce cellular damage.
- Cellular damage/dysfunction promotes nucleation at moderate supersaturation (or in a metastable state).
- Cellular damage leads to exposure of crystal binding substances on cell surface promoting crystal attachment to basement membrane.
- Crystal retention then leads to stone nidus.
- Inflammatory and other processes in response to the injury produced by the crystal itself produce migration of crystal which then establishes itself as a stone nidus which then forms the basis for a Randall's plaque.

The questions here are:

- Why does tubular cell injury produced by others (e.g. drugs) not lead to the cascade described and produce stones?
- What are the steps between the formation of the stone nidus in the interstitium and Randall's plaque?
- How does the nidus, presumably formed around the area of the loop of Henle, move to the sub-epithelial area?

Macromolecules

Professor Ryall (whose paper is unfortunately not included in this issue) argues that macromolecules are the real key – no macromolecules, no stone. The argument is based on:

- Macromolecules affect (and indeed are essential) crystal nucleation, growth, aggregation and cell attachment.
- They are an essential part of cellular injury.
- Stone are not an inevitable consequence of cell injury. Many others (e.g. drugs), after all, cause cell injury but may not necessarily produce stones.

The questions to be answered here are:

- Whilst macromolecules may be the key to the process from crystal formation to cell attachment, what is their role in the ultimate stone formation. After all, crystal attachment is still a microscopic event—remember, stones are macroscopic.
- Even if we accept that drugs etc. produce cellular damage but do not produce stones, there are still two more questions in this area to be answered. Is it because such damage does not invoke macromolecules—if not, why? Or is it because macromolecules are invoked but stones are not produced because there is no associated supersaturation? If the latter is accepted, surely the key to stone formation is supersaturation.

Conclusion

Debate such as this has long been overdue. It is entirely possible that none of the above is the key to stone formation but is the final stage of a process that was initiated by something else which may be the real key. However, there is an even more fundamental question that needs an answer. Is stone formation a disease of renal parenchyma (which implies that the process occurs in the tubules) or renal calyx and the sub-epithelial area of renal calyx? What is wrong with the theory, some may argue, that stones form because damage occurs locally in the sub-epithelial area of papilla which produces dystrophic calcification. Supersaturation then takes over to produce a stone. Maybe macromolecules are also needed in this process. The debate will no doubt continue.