

# The relevance of Randall's plaques

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## ABSTRACT

The pathophysiology of nephrolithiasis is not fully understood. The pioneering work of Alexander Randall in the 1940s sought to clarify our understanding of stone formation. This review traces the inception of the theory of Randall's plaques and the refinement of the hypothesis in the early days of kidney stone research. It then reviews the contemporary findings utilizing sophisticated investigative techniques that shed additional light on the pathophysiology and redefine the seminal findings of Dr. Randall that were made 70 years ago.

**Key words:** Kidney, stone, urolithiasis

## INTRODUCTION

Renal calculi have been plaguing humanity since the advent of civilization. Alexander Randall himself commented on the discovery of ancient human remains with evidence of a calcified mass in the pelvis, believed to be a renal stone.<sup>[1]</sup> The lifetime incidence of kidney stones is 5% in women and 12% in men of the United States, with an ever-increasing prevalence worldwide.<sup>[2,3]</sup> Untreated kidney stones can cause devastating morbidity and recur frequently. They pose a significant medical economic burden, totaling around \$2.1 billion annually. The majority of kidney stones consist of calcium oxalate, followed by calcium phosphate, uric acid, cysteine, and struvite stones.

Many factors influence the development of a stone including diet, genetics, environment, and comorbid

conditions. Although much headway has been made in the treatment of renal calculi, there is still much to learn regarding their genesis. Alexander Randall was an ardent believer that renal calculi were only an advanced symptom of a much deeper underlying pathology. Thus, he focused his work in trying to find the initiating lesion, the small 1-2 mm papillary calcification believed to be the nidus of some kidney stones, which is now eponymously referred to as Randall's plaque and affects patients of all ages.<sup>[4]</sup>

## HISTORY OF RANDALL'S PLAQUES

Alexander Randall began his career as the student of Hugh Howard Young at the Brady Institute at Johns Hopkins, Baltimore. During his tenure there and at the University of Pennsylvania, he contributed to the field of urology, particularly in the realm of obstructive uropathy secondary to prostatic hyperplasia. However, his most lasting and eponymous contribution was in the field of urolithiasis through his seminal work in the examination of the subpapillary deposits that bear his name.

In a lecture at the New York Academy of Medicine in 1944, Randall recounted the day he and his colleagues began to discuss their collective knowledge of renal calculi and their provenance. He recalled that in 1926, at the American Association of Genito-Urinary Surgeons, there were five questions that needed to be answered with respect to stone formation, the first of which was knowing where the stones initially began to form.<sup>[5]</sup> This question spurred Randall's exploration of the renal pelvis. He began this investigation by attempting to induce renal stones in an animal model; however, given the inconsistency

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in the results, he was compelled to change his research paradigm.<sup>[6]</sup>

Instead of trying to incite injury, he realized the deficit in knowledge regarding the renal papilla, the area that he suspected was the root of renal stones, and began a more formal study of cadaveric kidney lesions. In his famous case series, he examined 1154 pairs of kidneys, excluding those that had obvious gross pathologies such as pyelonephritis, and found that 19.6% of them showed evidence of a calcified lesion in at least one renal papilla. In this series, Randall was able to observe 65 kidneys with a primary renal stone attached to the papillary plaque.<sup>[6]</sup>

In a different case series, he examined 265 renal stones that were either passed spontaneously or by ureterolithotomy. He noticed that 40% of these showed evidence of a smooth region on one facet of crystalline stones that appeared to be of a different mineral composition than the rest of the stone.<sup>[6]</sup> It was theorized that this was the stone's mural attachment.

During analysis of these stones, he was able to identify a purely calcium oxalate black stone attached to a white calcium carbonate/calcium phosphate base.<sup>[1]</sup> The group then undertook the characterization of the pathologic features of affected papillae and plaques. They were able to identify the different stages in the genesis of plaque, starting from the derangement of blood vessels in the region of the papilla midway between the tip and base, the preponderance of dense connecting tissue, the degeneration of the epithelium covering collecting tubules, and the deposition of calcium in the basement membrane of the papilla.

Randall noted evidence of severe atherosclerosis in the irregular blood vessels in this area. As the epithelium and connective tissue overlying these calcium deposits degenerates further, the plaque is able to become a base over which the subsequent stones may form. This base comprises spherules of calcium deposited irregularly within the renal papilla in the membrane of the collecting tubules and interstitial spaces, which was termed Papillary Lesion Type I.<sup>[6]</sup> Papillary Lesion Type II was a less commonly characterized inspissation of the collecting tubules, and thus not an extratubular lesion like Type I. One major difference between these two lesions is that Type II is predominantly found to affect several papillae at a time and has a quicker presentation similar to infarction, unlike Type I lesions, which have a slow natural history. Lastly, Randall reasoned that the inciting damage to the collecting tubule basement membrane was caused by a high concentration of excreted toxins in the urine, because of the natural filtering property of the kidney.<sup>[6]</sup>

Although there were several theories that postulated the origin of stones, including stasis, infection, hypovitaminosis leading to uroepithelial injury, derangement of the

saturation of urinary solutes and colloids, and parathyroid hyperfunction, Randall's group was able to demonstrate that an inciting lesion was necessary for the formation of stone. Furthermore, the group was able to discount the necessity of infection in lithogenesis, as at no point during their series did they find any signs of infection.<sup>[5]</sup>

Several of Randall's contemporaries worked to test his proposed theory of the per-calculus lesion. Kjolhede and Lassen examined a Danish series of 135 necropsy specimens and 263 kidneys. They performed macroscopic and histologic studies of their samples.<sup>[7]</sup> The group studied an average of 7.2 papillae per kidney and found papillary deposits in 86 cases. In their series, 49 cases (36.7%) showed no evidence of macroscopic or microscopic calcium deposits. The group described four patterns of extratubular calcium deposition, which they concluded were of Papillary Lesion Type I from Randall's description. Only five of their cases (3.7%) showed intratubular plugging, or Type II lesions. Kjolhed saw evidence of epithelial degeneration in the tissues surrounding these calcium lesions and concluded, as Randall had, that this degeneration is likely the initial presenting pathology that leads to calcium deposition and plaque formation. Furthermore, they too observed that the calcium deposits were located initially in the basement membranes of the renal tubules.<sup>[7]</sup> An interesting finding in this series was the evaluation of patients' comorbidities and their correlation to renal plaques. Of note, the authors found that patients with calcium deposition had a history of atherosclerosis, renal infection, and urinary stasis more frequently than the patients without deposition. They found no relationship between plaque presence and age, sex, circulatory disease, digestive disease, chronic disease, or malnutrition.<sup>[7]</sup> The group also examined the relationship between calculus presence and evidence of plaque. They found only 14 cases of renal stone in their series, 10 of which were primary. In six cases (23.3%), they observed stone but no evidence of papillary plaques. In 8 of 14 cases, they found both stone and plaques. These observations led them to conclude that papillary deposits do not give the complete explanation for the story of renal stone formation. Rather, they were the nidus for a small percent of renal stones; essentially plaques facilitated stone formation when they were present, but stones likely formed through another pathologic process.<sup>[7]</sup>

Vermooten examined the pathophysiologic reason behind lithogenesis, as it is related to Randall's plaques. In his own series of over 1000 pairs of necropsy kidney specimens collected in Johannesburg, he was able to fully and serially section the papillae of 20 such pairs and examine the progression of the plaques and their place within the renal architecture.<sup>[8]</sup> Vermooten found that the pathologic entity that enabled the formation of plaques was the collagen fibers in the basement membranes of the collecting tubules, rather than the degenerating epithelial cells. His argument was

that Randall's hypothesis of a highly concentrated toxin damaging the epithelial lining and leading to injury was of lesser significance, and perchance an incidental finding, than the defective collagen within the affected basement membranes. Furthermore, Vermooten noted evidence of poor vascular supply in his dissected specimen, with many of the calcium deposits found perivascularly and in the interstitial spaces. He concluded that senescence of the tissue was likely the cause for the defective collagen, deposition of new and disordered collagen fibrils, decreased and degenerating vascularity, and subsequently, much like in the formation of bone, deposition of calcium onto this new tissue matrix. He summarized that although Randall's theory of injury due to toxin concentration could be an explanation of some plaque formation, the relative frequency of plaques among the population suggested that the true underlying pathology was damage to the collagen network due to any cause and was related to increasing age.<sup>[8]</sup>

In 1975, Prien also tried to consolidate the knowledge of calculus pathology as it pertained to Randall's plaques. He acknowledged that most investigators of the time agreed that the subepithelial calcium depositions were truly an explanation and nidus for the formation of renal stones, but certainly not the reason behind a majority of stones. In his own investigative series of over 100 renal specimens, he found only one example of a calcium oxalate stone attached to a renal papilla, but found evidence of plaques in 13 kidneys. Furthermore, Prien examined cross sections of papillae and stone, and found that their eccentric nucleation and mineral composition did support the theory that they began from a mural attachment.<sup>[9]</sup>

The improved characterizations of the crystal component of stone made by Randall's successors seem to shed more light into the pathology of renal stone development. However, it was the technical limitations faced by Randall that perhaps led to the incomplete theory of lithogenesis related to his plaques.<sup>[10]</sup>

## CONTEMPORARY STUDIES THAT SUPPORT THE ROLE OF RANDALL'S PLAQUE IN LITHOGENESIS

### *Endoscopic and metabolic studies*

With the advent of more advanced imaging techniques, the field of stone disease has gained a deeper understanding of Randall's plaques and the pathophysiology of lithogenesis. In particular, living kidneys can be imaged endoscopically for the occurrence of Randall's plaques and their presence can be correlated to clinical and metabolic events in the patients.

Reevaluating Randall's initial analysis, Matlaga *et al.* evaluated 23 known calcium oxalate stone formers and endoscopically mapped 172 renal papillae. They found that 91% of these contained plaques, and that all kidneys examined had at least one papilla that was affected. Moreover, they found

that stones were attached to 49 papillae, and of these papillae with stone attachment, 44, or 90%, had evidence of plaque remnant on the papillae. The authors noted that this number may have been higher and that the plaque could have been removed along with the attached stone.<sup>[11]</sup> Overall, this study found that 48% of stone-burdened kidneys had attached plaques, as opposed to 5.6% reported in Randall's series.<sup>[6]</sup> Moreover, the authors found endoscopic evidence of dilated duct orifices after detachment of stone, which they believed were uncalcified tubular remnants after plaque detachment, a finding that supported the reports by Cifuentes Delatte *et al.* of such remnants on spontaneously evacuated calculi.<sup>[12]</sup> In conjunction, these studies support Randall's initial hypothesis that lithogenesis starts with an interstitial lesion in the papilla that forms a nidus for stone attachment.

Low and Stoller were one of the first groups to utilize endoscopic imaging in their examination of renal papillary calcifications.<sup>[13]</sup> Their case series included 64 patients who had calyceal mapping for Randall's plaques. Of these, 57 underwent mapping during endoscopic procedures for stone removal, 21 ureteroscopically and 36 percutaneously. The remaining seven patients had endoscopic procedures for resection of upper tract malignancy and evaluation of lateralizing hematuria. A mean of 7.1 calices were examined in each patient. Low and Stoller observed two patterns of calcifications in the calices: Central and diffuse, each occurring without preference for location and showing no correlation for age, sex, or stone composition. The pattern types also did not differ between patients with stones and those without stones. Furthermore, they found that 74% of stone formers had evidence of these plaques versus only 43% of the patients who underwent endoscopic evaluation for reasons other than stone. More importantly, they found that patients with uric acid or calcium oxalate stones had a 100% incidence of Randall's plaques on mapping, while those with calcium phosphate, cystine, and struvite had an incidence of Randall's plaque of 88%, 33%, and 20%, respectively ( $P = 0.0004$ ).<sup>[13]</sup> This study was important as it provided support for the theory that different stones have different primary pathogenesis.

In a later study, Low *et al.* examined a cohort of 143 patients (124 stone formers and 19 non-stone formers) by the same method as above and also looked at their metabolic and urinary characteristics<sup>[14]</sup> on the premise that the urinary milieu in addition to Randall's plaque presence provides the necessary conditions for lithogenesis. In the stone former group, 85 patients underwent 24-h urine collection and urinary evaluation for calcium, oxalate, citrate, uric acid, sodium, magnesium, and urinary volume. Again, 73% of stone formers showed evidence of Randall's plaques versus only 32% of non-stone formers ( $P = 0.001$ ). Furthermore, plaque was found more frequently in stone formers with calcium oxalate stones than in other stone formers and non-stone formers ( $P = 0.042$ ). Similar to their previous study,

plaque was evident most frequently in calcium oxalate stone formers (77%) than in those with cystine or struvite stones (50% and 29%, respectively). Although all the urinary risk factors that were investigated showed a trend toward a higher association in patients with plaques, the relationship was not statistically significant in this study. The factor that was most nearly significant in relation to plaque presence was the presence of hypercalciuria. This study provided further evidence to the importance of Randall's plaques on the formation of calcium oxalate stones in particular. More interestingly, it introduced the idea of correlating endoscopic patterns of plaque to Randall's original classification of Type I and II depositions.<sup>[14]</sup> Papillary biopsies were later studied by other groups.<sup>[15]</sup>

Continuing the investigation of metabolic correlates to Randall's plaques, Kuo *et al.* found that the calcium levels in urine and urinary volume correlated with the extent of papillary plaque burden.<sup>[15]</sup> On the principle that hypercalciuric fluid in the collecting tubules along with increased water extraction create the appropriate microenvironment for calcium deposition, the group performed extensive mapping of renal papillae using flexible nephroscopy. Their series included 18 patients, including 14 calcium stone formers and 4 non-stone formers. Their control group of non-stone formers had radical nephrectomies for renal cell carcinoma, and their papillary examination was performed *ex vivo* on surgical specimen. The entire cohort of stone formers had 24-h urine collections on native diets after cessation of medications that altered calcium metabolism, while the control cohort had 24-h urine samples collected prior to surgery. The group measured urinary volumes and pH, and the levels of calcium, oxalate, citrate, sodium, potassium, chloride, sulfate, ammonia, creatinine, and uric acid. The elegant study video recorded the entire nephroscopy procedure, and the surface area of plaque was determined by an algorithm that measured the number of pixels taken up by each plaque compared to the pixels taken up by the entire papilla. They found that plaque surface area per papilla was significantly greater in stone formers than in non-stone formers (7.6% vs. 0.6%,  $P = 0.011$ ), and that high calcium levels, low urine volumes, and low pH correlated with plaque coverage. Their study illustrates that a simple urinary environment with the right characteristics facilitates the creation of Randall's plaques.<sup>[15]</sup> Furthermore, it addressed the criticism of Randall's original work being performed on a large sample of necropsy specimen without clinical stone disease correlation, as this cohort of patients underwent papillary biopsies that corroborated the existence of interstitial deposition of plaques.

Continuing their evaluation of this group of patients, Kim *et al.* investigated the relationship between plaque burden and clinical stone disease, and found that the two had a significant correlation.<sup>[16]</sup> This report completed more of the story linking Randall's plaques to calculus formation. In their

study, the clinical stone histories of 15 of the above patients who had a history of calcium oxalate stones correlated with the endoscopic evidence of their plaque burden. The group found a significant and independent correlation between the duration of stone disease and the mean plaque surface area with stone events (0.677 and 0.620,  $P = 0.003$  and 0.008, respectively), and the correlation still stood even when adjusting for disease duration. Moreover, they found that plaque surface area and stone disease duration did not have a significant correlation ( $P = 0.257$ ), disputing the hypothesis that given any length of time, plaque burden, and thus stone incidence, will increase.<sup>[16]</sup> These results beg the question of what then predisposes some patients to form papillary calcifications and develop substantial plaques, while others do not.

### *Radiographic studies*

An adjunct to endoscopic imaging of Randall's plaques is the use of high-resolution radiography in the detection of renal papillary calcifications. Stoller *et al.* examined 50 cadaveric kidneys using microfocal spot magnification radiography, similar to that used in mammography, to detect microcalcifications.<sup>[17]</sup> They also performed histologic examinations to correlate their plaque radiographic results to tissue samples, as well as examined the clinical histories of 46 patients for the presence of renal stones, cardiovascular risk factors, obesity, and history of cardiovascular disease. They found that 57% of the renal units studied had radiographic evidence of Randall's plaque, as compared to the 19.6% initially detected by Randall.<sup>[6]</sup> This study also corroborated Randall's description of basement membrane calcifications in the collecting tubules and papillary interstitium. The only other correlate they were able to find to Randall's plaque was a history of hypertension, in which 83% of samples from hypertensive patients had evidence of plaque versus 52% of those without hypertension ( $P = 0.05$ ). Interestingly, and perhaps as a function of the state of medical at the time, 18 of their 50 patients had a history of acquired immunodeficiency syndrome, although no correlation to Randall's plaque presence could be made. A major limitation of this cohort, similar to those that Randall originally reported, was that only two patients had a known history of nephrolithiasis; therefore, no conclusions could be drawn regarding the role that Randall's plaques played on lithogenesis at the time.<sup>[17]</sup>

As technological advances enable us to make characterizations by multitude of methods, it is important to define appropriate criteria for which radiographic findings constitute plaques versus stone or other entities such as nephrocalcinosis.<sup>[18]</sup> Miller *et al.* highlight the difficulty in making such a distinction, but also its necessity as it can lead to reduced morbidity in stone patients. They also propose that perhaps the diagnosis of nephrolithiasis can only accurately be made endoscopically to differentiate from radiographic findings of nephrocalcinosis.<sup>[18]</sup>

## PATHOPHYSIOLOGIC MECHANISM OF RANDALL'S PLAQUE FORMATION

The role of Randall's plaques as the base upon which calcium stones form has been investigated by several groups; however, it is yet to be discovered why Randall's plaques themselves are created. Insight into this process can lead to novel methods of stone disease prevention. Evan *et al.* looked into the location within the kidney that is most likely to be insulted by Randall's plaque.<sup>[19]</sup> They studied 19 patients with a history of at least two prior stones composed mostly of calcium oxalate, four of which had undergone intestinal bypass surgery, but the rest had no history of known metabolic derangement. They used four patients with no prior history of personal or familial stones as their control population. All patients underwent two 24-h urine collections and all had papillary biopsies during endoscopic procedures for stone removal or of their excised kidney for non-stone related causes. Tissue and stone specimens were analyzed using standard histology protocols, and X-ray diffraction spectroscopy and infrared microspectroscopy. Evan *et al.* found calcium deposits in the interstitial spaces following the thin loops of Henle and vasa recta in calcium oxalate stone formers with no other comorbidities. They found no evidence of cortical calcifications or of intratubular deposits. Interestingly, these findings did not occur in patients with stones after intestinal bypass, and it was concluded that these patients form stones by a different pathophysiologic mechanism than the common calcium oxalate stone formers.<sup>[19]</sup> This was again emphasized by Matlaga *et al.* in later investigations.<sup>[20]</sup> Moreover, non-stone formers in this cohort also did not show evidence of Randall's plaques. The greatest contribution of this work was to show that all lesions originated around the basement membranes of the thin loops of Henle, refining Randall's original observations. The authors also observed that collagen and mucopolysaccharide matrix around these membranes forms a suitable environment for crystallization of minerals in the urine,<sup>[19]</sup> and such an organic matrix is crucial for the formation of stones, as others have subsequently examined.<sup>[21,22]</sup>

Reid *et al.* also looked at the biomacromolecular milieu of renal calculi and Randall's plaques.<sup>[23]</sup> They examined 28 apatite and mixed apatite–struvite stones using nuclear magnetic resonance spectroscopy to analyze the mineral — organic interphase. Their technique previously showed the interactions between glycosaminoglycans (GAGs) and apatite on calcified tissues like bone, dentine, and atherosclerotic plaques. The method required a bulk of organic material, and because of the small area of Randall's plaque attachments to renal stones, only 10 of their samples had sufficient material for analysis. Despite this, they were able to show the same interactions between apatite stones and GAGs. As Randall's plaques are composed of phosphatic calcifications, their work provides some insight

into the original process that initiates plaque formation. Furthermore, it also points toward a possible targeting mechanism between nascent calcifications and subepithelial plaques.<sup>[23]</sup> The epithelial covering that initially overlies Randall's plaques provides a rich environment of GAGs and collagens that can act as the organic matrix to aid stone formation and attachment. Lastly, they showed similarities between these mineral–protein complexes and those of other mineralized tissues; therefore, it is feasible that therapies that prevent atherosclerotic processes may also aid in the prevention of renal calcifications.<sup>[23]</sup> This was a preliminary study, and much further work is needed in the field, particularly studies that look at distinct populations of stones.

The proteome of renal calculi has been investigated extensively by several groups. Canales *et al.* reported that no significant difference was noted in the overall protein milieu between calcium phosphate and calcium oxalate stones.<sup>[21]</sup> Using infrared spectroscopy and mass spectroscopy on the proteins extracted from pulverized calcium oxalate and calcium phosphate stones, the group was able to identify 113 distinct proteins. While 64 proteins were found in at least two stones, 42% of these were part of the inflammatory cascade, supporting the theory that an inflammatory state promotes stone growth.<sup>[21]</sup>

Khan *et al.* also investigated the pathophysiologic mechanism of Randall's plaque formation.<sup>[24]</sup> Stemming from the similarities between Randall's plaques and vascular calcifications, they aimed to determine the substrate that promoted calcium phosphate crystallization. From their cohort of 15 cold cup renal papillary biopsies, they were able to detect spherical subunits that contained calcium phosphate and that aggregated with collagen to form tissue calcifications in basement membranes of the loops of Henle that extended into the papillary interstitium. Cellular degradation products are also a part of this process, perhaps indicative of underlying inflammatory states. This process was similar to ectopic calcification that occurs in various soft tissues after injury. Although more work needs to be done on this topic, this study provides a unique look into the origins of Randall's plaques.

Lastly, a novel hypothesis arose regarding the similarities between Randall's plaques and vascular calcifications. Stoller *et al.* proposed that the initial insult was indeed a vascular event that set the cascade for tissue mineralization. In a review of the literature and from stone analysis of 11 of their own patients undergoing percutaneous nephrolithotomy, they highlight inconsistencies in the current theory lithogenesis stemming from solely a urinary insult and propose that it is plausible that the delicate vasa recta undergo a physiologic insult from hypoxia and hyperosmolarity, that, in concordance with the proper urinary environment, could lead to Randall's plaque formation.<sup>[25]</sup>

## CONCLUSIONS

Despite the early technological limitations of Randall's era, he was able to provide the building blocks of a theory that has been substantiated in the recent decades. Although Randall's plaques may not be the entire explanation for lithogenic phenomena, they do play an important role in a subset of patients with calcium oxalate stones, whose incidence has been increasing in recent decades. Essentially, an insult to the basement membranes of the loops of Henle caused by a yet unknown etiology couples with the right matrix proteins and urinary mineral environment and creates an inflammatory state that is prolithogenic. This cascade has been validated by numerous endoscopic, radiographic, and molecular studies *in vivo*, and in animal models, much work is still left to be done. Nonetheless, it is incredible that with only a hand lens and five questions at his disposal, Randall was able to reach conclusions that form the basis of stone research nearly a century later.

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