

## Introduction

*“Surgery, like other branches of the healing art, has followed in its progress zigzag paths, often difficult to trace. Now it has seemed to advance by orderly steps and, through the influence of some master mind, even by bounds; again it has stumbled apparently only from error to error, or has even receded; often there has appeared some invention or discovery for which time was not ripe and which had to await for its fruitful application, or perhaps its re-discovery, a more favorable period, it might be for centuries.”* [1]—William Stewart Halsted, 1904

Urinary calculi are a complex group of biomaterials that can and do occur anywhere within the urinary tract. Stones have afflicted humans since the first recorded histories of medicine. Ancient writings by the Babylonians and the Egyptians mention the clinical findings and the treatment of urolithiasis, and Shattock studied in detail an ancient bladder stone from a predynastic Egyptian boy. Hippocrates in his “Physician’s Oath” stated, *“I will not cut, even for the stone, but leave such procedures to the practitioners of the craft”* [2]. Hippocrates was the first to attribute dehydration and cystitis as important etiological factors in stone disease [3]. His treatise *On Diseases Book IV On Calculi of children, i.e., lithiasis*, will be discussed in some detail [3]. Aulus Cornelius Celsus is primarily regarded for his encyclopedic treatises. We will discuss in some detail his accounting of surgery for bladder stones [3]. Claudius Galenus described renal colic in the book VI of *De Locis*

*Affectis* and is considered a naturopath as he attempted to manage stone disease with wine, honey, parsley, and caraway seeds [3]. Lanfranc of Milan was a surgeon of some renown and eventually was attracted to Paris and published on surgical methods in 1270. Henri de Mondeville and Guy de Chauliac followed in his wake and also left lasting surgical legacies from the Middle Ages. Marianus Sanctus presented a new method of performing perineal lithotomy with the aid of more sophisticated instruments in 1522, called the *“great apparatus”* or *“sectio marianus”* [4]. Frère Jacques devised the lateral method of lithotomy and demonstrated the new method throughout much of Europe in the early 1700s. William Cheselden dissected human cadavers and improved upon the method of perineal lithotomy. Civiale and Bigelow pioneered methods of minimally invasive lithotripsy, some of which can still be found in operating rooms. The work by Karl Wilhelm Scheele, William Hyde Wollaston, Alexander Marcet, Antoine F. Fourcroy, and Nicolas Louis Vauquelin laid the foundations for the current pathophysiological concepts and medical management of stone disease; they proposed changing the stone-forming milieu by administering alkalis or acids to arrest and dissolve urinary calculi. The Industrial Revolution brought about changes in the quality of life and raised people to different social classes, which in turn lead to a change in dietary habits. All these changes have been associated with a paradigm shift of occurrence with urinary calculi, with bladder stones

becoming less common and upper urinary tract stones becoming more so. This trend still persists and can be shown to be true if one were to compare the incidence of urinary calculi in the industrialized/Western nations with those of the developing nations.

This change to upper tract development of urinary calculi necessitated a change in the management strategies of urolithiasis. One of the sentinel medical developments of the twentieth century and perhaps a prime example of the civilian benefits of military research (the peace dividend) was the introduction of extracorporeal shock wave lithotripter by Dornier GmbH, a German aerospace company. There are lithotriptors in nearly every country of the world with a plethora of available technologies now available to treat most stone sufferers since the first human treatment by Christian Chaussy on February 20, 1980, in Munich. The current trend in this remarkable device's evolution is to make them smaller, more energetic, with a wider range of treatment settings to minimize the need for anesthesia and to make them more multifunctional than the older "bathtub" units.

Some investigators believe that the impact being made in our ability to manage urolithiasis represents the combined benefits of the surgical and medical advances in understanding the pathophysiology, diagnosis, and treatment of urolithiasis. As we venture forth into the changing era of the practice of medicine, the state-of-the-art approach to the management of urolithiasis would be incomplete if it did not include a combination of medical and surgical intervention such that not only would the acute stone episode be addressed but equal importance would be given to preventive measures (metaphylaxis). It is now known that metabolic or environmental etiologies of nephrolithiasis can be found in approximately 97 % of patients evaluated for their stone disease. Stone disease is a complex problem and requires an equally complex methodology to handle the subtle differences for every individual patient. Stone disease remains on the rise in the USA possibly affecting one out of every seven individuals, costing the healthcare system billions of dollars annually.

## Not Created Equal

In 1963 Prien published the incidence of the various stone types seen in the USA (Table 2.1) [5], and updates have been modernized by Dr. Pearle's publication on urolithiasis in Urologic Diseases in America Project [6]. The majority of stones are composed of calcium oxalate, 70–80 %. The remainder contain calcium phosphate salts, uric acid, magnesium ammonium phosphate hexahydrate (struvite), and rarely the amino acid cystine. Although these five stone types represent the majority of all reported stones in the USA, they are just a few of the reported substances that are capable of precipitating as a urolith. Calcium oxalate stones dominate modern stone series in incidence in two primary forms, often admixed. Whewellite (WH) is calcium oxalate monohydrate and is more common. Weddellite (WE) is calcium oxalate dihydrate and is the crystal moiety that is commonly seen in urinalysis specimens. The calcium oxalate type is crucially important to urologists treating the calculus as whewellite stones are more likely to fail SWL than are weddellite stones. There is no preoperative modality to identify which type of stone is present in a given patient. In pooled stone series, calcium oxalate stone was present in  $73 \pm 7$  % of all stones.

Calcium phosphate stones are much more heterogeneous. They are rarely pure components within stones, most commonly complexed with calcium oxalate. The exception is brushite (BR), calcium hydrogen phosphate. Stones composed predominately of calcium phosphate approximate 10 % of the total. These patients should prompt full metabolic evaluation by the treating physician as calcium phosphate stones represent a harbinger of active stone disease and significant underlying medical disorders. Brushite in particular should be a trigger to further investigations to identify distal renal tubular acidosis, primary hyperparathyroidism, and sarcoidosis. In addition, pure brushite calculi represent the second most difficult stone to fragment with SWL, predisposing to secondary interventions.

Magnesium ammonium phosphate hexahydrate (struvite) are the bacterial-induced or infectious

**Table 2.1** The timeline for the comprehensive history of urolithiasis

Timeline for urolithiasis (BCE=before current era, CE=current era)
– 1st known stone formed (5500 BCE, female bladder stone, Mesolithic)
– 1st known kidney stone (circa 3300 BCE)
– Hippocrates (Oath? 460–370 BCE)
– Aristotle (384–322 BCE)
– Epicurus (341–270 BCE) suffered from kidney stones and colic
– Aulus Cornelius Celsus 25–50 CE
– Galen (131–201 CE)
– Paul of Aegina (625–690 CE)
– Indian Vedas (Sushruta ?400 CE)
– al-Razi (Rhazes 890–923 CE), al-Avicenna 980–1036 CE), al-Zahrawi (Albucasis 1050–1106 CE)
– Henri de Mondeville (c1260–1316)
– Guy de Chauliac (c1300–1368)
– Philippus Aureolus Theophrastus Bombastus von Hohenheim (Paracelsus 1490–1541)
– Pierre Franco (1500–1561)
– Felix Würtz (c1500–1590)
– Battista da Rapallo and Mariano Santo da Barletta (De LapideRenum 1535) (1488–1577)
– Lanfranc (Pierre Franco 1500–1561)
– Ambroise Pare (c1510–1590)
– Andreas Vesalius (1514–1564)
– William Harvey (1578–1657)
– Frere Jean de Beaulieu (Jacques 1651–1714–1719), Claude-Nicolas Le Cat, Jean Baseilhac (Frere Come 1703–1781)
– Johann van Beverwijck (1594–1647)
– Thomas Sydenham (1624–1689) & Herman Boerhaave (1668–1738)
– Rev. Stephen Hales (1677–1761)
– William Cheselden (1688–1752) fastest lithotomy at 54 s (mortality 17 %)
– Robert Whytt (1714–1767)
– Joanna Stephens (£5,000 1739) stone formula
– John Hunter (1728–1793)
– Erasmus Darwin (1731–1802)
– Carl Wilhelm Scheele (1742–1786)
– George Pearson (1751–1828)
– William Hyde Wollaston (1766–1826)
– Alexander Marcet (1770–1822)
– <b>English school</b> [George Owen Rees (1813–1889), Henry Bence Jones (1813–1873), John Howship, William Henry (1774–1836), William Prout (1785–1850), Golding Bird (1814–1854), Richard Bright(1789-1858)], <b>French school</b> [Felix D’Azyr (1748–1794) Antoine F. Fourcroy (1755–1809), Nicolas L. Vauquelin (1763–1829) Gay-Lussac (1778–1850), F. Magendie (1783–1855)]
– Jean Civiale(1792–1867) (January 13, 1824—lithotrity) Necker Hospital in Paris
– John Yelloly (1774–1842)
– Sir Henry Thompson (Victorian urologist 1820–1903)
– Alex Copland Hutchison (1830)
– Henry Vandyke Carter (1831–1897)
– St. Peter’s Hospital for Stone (1860)
– Henry Bigelow (1818–1870) Litholapaxy
– J. Swift Joly (1876–1944)
– Eugene F. DuBois (1926) parathyroid disease and stones (Captain Charles Martell) (1882–1959)
– Alexander Randall (1883–1951)
– Fuller Albright (1900–1969)
– William H. Boyce (1918–2012)
– Birdwell Finlayson (1932–1988)
– Martin Resnik, Joseph Segura, Steven Streem, Lynwood Smith, Bill Robertson
– Fred Coe, Charles YC Pak, Rosemary Ryall, Saeed Kahn, George Drach, Neil Mandel
– Ralph Clayman, Arthur Smith, Glenn Preminger, Christian Chaussy, James Lingeman, Marshall Stoller, Hans Tselius, John Asplin, Andrew Evan, Dean Assimos, Margaret Pearle, John Lieske, etc.

stones. These stones are often heterogeneous with varying amounts of other mineral (carbonate apatite) or proteinaceous matrix present. These stones represent 2–20 % of the total population and are twice as common in women as in men. These stones are classically associated with urease-producing infections, most commonly *P. mirabilis*. Struvite calculi account for most of the staghorn stones encountered in clinical practice.

Purines and their salts (uric acid, uric acid dihydrate, monosodium urate, ammonium acid urate, and rarely xanthine or 2,8-dihydroxyadenine) account for 5–10 % of stones. The calculi occur because humans lack the enzyme to convert uric acid into the freely soluble allantoin. Since human urine is predominately acidic, depending upon the saturation, normally between 500 and 600 mg/L, precipitation is always possible. In addition, another capability of uric acid crystallization is its ability to propagate crystal deposition with calcium oxalate, termed heterogeneous nucleation. About 10 % of calcium oxalate stone formers have only hyperuricosuria as the principal metabolic abnormality. Uric acid stones and their salts are truly radiolucent which underlies the difficulties with diagnosis and therapy. Standard radiographs are not helpful so ultrasonography, intravenous urography, or, in difficult cases, non-enhanced renal computed tomography (CT) must be used to follow these individuals. Secondary uric acid lithiasis should always be evaluated to rule out primary pathologic processes such as gout and myeloproliferative disorders.

Cystine stone disease is the least common approximating 1 % of patients. This is an autosomal recessive disorder affecting membrane transport of dibasic amino acids. Cystine stones are radiopaque secondary to their disulfide bonds. There is a propensity for these stones to occur in younger individuals, second to third decades, and two-thirds are pure whereas one-third contain a mixture with a mineral content.

Before leaving this discussion of stone types, recent trends of iatrogenic-induced urolithiasis and rare stone types should receive mention. Triamterene-containing stones have been noted to be increasing in prevalence in the USA. This potassium-sparing diuretic is often used in

combination with thiazides for treating hypertension. Should a patient pass a stone while taking this drug it should be suspected and the drug discontinued. Silicate is another rare compound found in human stones. It is utilized in many pill-forming processes but found in largest concentration in some antacids (magnesium trisilicate). Sulfonamides were a concern three decades ago when poorly soluble, high dose regimens were popular and stone formation was a problem. Now trimethoprim-sulfamethoxazole is rarely associated with stone formation in patients exposed for prolonged periods, such as in HIV sufferers. In this same population, newer protease inhibitors such as indinavir have been increasingly associated with stone formation. Indinavir is known to be poorly soluble in urine, and rapid precipitation with symptomatic stone formation has been reported in at least 3 % of patients on this drug. About 1–2 % of patients taking acetazolamide (Diamox) and the migraine drug topiramate (Topamax) also induce calcium phosphate-type nephrolithiasis.

Rare stone types may result from inborn errors of metabolism of nucleic acids on the pathway to uric acid production. Two such stones are xanthine and 2,8-dihydroxyadenine, which are both radiolucent, exceedingly rare, and occur more commonly in children. Stones suspected of being uric acid that do not respond to chemodissolution by alkali should be considered as one of these two types. The rarest stone type of all will be discussed in a separate historical chapter (Chap. 26). Large stones or record-setting stones and procedures will draw our attention to Chap. 27. The cult of interest in such things as the fastest, farthest, most painful, and largest reflects mankind's fascination with the bizarre that will be the focus of that chapter.

In summation there exists five common stones that afflict humans but other rarer types should not surprise anyone interested in urolithiasis. These will be presented in some detail in Chap. 29 on Modern Stone Science. This underlies the importance of having the patient retrieve the calculus for stone analysis. It is important for the physician to be aware that the correct diagnosis of the stone type is directly related to the reference

laboratory's methods to perform the analysis. That is to say, obtaining incorrect results of the stone's actual composition could be wrong if the laboratory is relying upon wet chemistry or polarized microscopy alone. In one recent study a range of 6–77 % correct analyses were achieved by wet chemical methods compared to 89 % for infrared spectroscopy.

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## Stones Through Time

The incidence of stones depends upon the region of the urinary tract that is discussed. For much of the history of stone disease, bladder stones have predominated. We will spend a good deal of time in this historical textbook talking about bladder stones. Most bladder stones from the past eras occurred in childhood and are now believed to have been largely due to the phenomenon of endemic bladder stone disease. This is caused by nutritional deficiencies that were elegantly worked out by dietary studies in India by Sir Robert McCarrison.

John Graunt spent a great deal of time studying the statistics compiled in the Bills of Mortality, and on February 5, 1662, he published his ninety-page summary of the facts with his commentary. This was distributed to members in attendance at a meeting of the Royal Society. The prevalence of stone disease was available for anyone to see, and it was accompanied by the mortality from surgical treatment and stark reminder of the dangers of medicine. Jean Civiale, a French surgeon who became interested in less invasive methods of surgically treating bladder stones, developed his transurethral methods of lithotripsy and began to gather statistics of mortality of his method compared to the standard perineal lithotomy. He presented his work before the Académie des Sciences; he compares his series of 257 patients to 5715 lithotomies. His expanded data showed that 6/257 patients with lithotripsy died (2.3 %) versus 1,141 or 20 % for lithotomy. The Académie responded with a written report on the use of statistics in medicine that has become a landmark paper in the history of medical statistics.

Matthew Dobson was the first to report upon a statistical inquiry on the incidence of stone disease in various parts of England. The number of patients admitted to the Norwich infirmary was thirty times higher than those admitted to Cambridge Hospital.

Another surgeon, Alex Copland Hutchison, wrote a treatise on stone disease on May 4, 1830, which presented the hypothesis that seafaring peoples such as sailors and townsfolk from seaside towns were less likely to develop urolithiasis. Though this work would go on to be questioned and eventually proven to be a product of selection bias, it was absolutely fascinating work as well as reading for this early period of epistemology.

In 1802, Fourcroy published his extensive research on stone disease and later did work with Vauquelin and began to encourage stones from all over France to be sent into a central registry for research purposes. They began one of the first epidemiologic databases for chemical evaluation and clinical correlation. In England this would fall to Golding Bird who also began to tabulate this data and report upon it in his published writings. Stones and clinical history began to be recorded, and the details could then be compared and evaluated. The only clinical medications proven to be efficacious were oral alkalis, and these were highly controversial.

At the end of the Industrial Revolution and the outset of the twentieth century, endemic bladder stones began to be systematically noted to have vanished throughout much of the world. During this time it was noted the nephrolithiasis was rising in the wake of improved living conditions and improved diet. Many an early investigator of urolithiasis at the outset of the twentieth century began to develop methods of studying these phenomena. J. Swift Joly gathered detailed information from all around the world, like an early American effort by Samuel Gross. They noted that certain regions of the world had higher rates of stone presentation than others. They began to dissect the data based upon geographical variations and diet. The first studies on water supply and the hardness of the water were performed in the eighteenth and nineteenth centuries and

showed a reverse correlation. Early modern studies confirmed these speculative studies of an earlier era.

## Lithology

The term lithology literally implies the knowledge of stones, and we are using it here to discuss the history of the theories of stone formation. The history of mankind's interest in the formation of urolithiasis begins with Hippocratic writings. The Hippocratics were probably a cult that was dedicated to the craft of medicine arising on the Island of Cos. One thought expostulated was that stones were caused "*when a child drinks impure milk*" [3]. The four humors were the underlying basis of health and disease. They believed that the impure milk could throw off the balance causing the formation of bladder stones, particularly in boys. In *Aphorisms* the authors were aware that sandy sediments form in a person's urine if they are suffering from the stone. In *On Airs, Waters, and Places* Chap. 9 attributes certain sorts of water as being bad for stone formers, whereas others from hot springs or the water from long rivers are beneficial. These authors also present a detailed hypothesis, "*And when the bladder suffers from such conditions it does not expel the urine, but concocts and heats it within itself. The finest part is separated off, and the clearest passes out and is discharged with the urine, while the thickest and muddiest part is collected and forms solid matter....*" [3].

Celsus gives a rather good account of the ancient history of lithotomy: "*If however, sometimes it appears that the stone cannot be extracted without lacerating the neck of the bladder, then the stone must be split up. For this reason, Ammonius, the inventor of this method, was surnamed "lithotomus"*" [3]. Galen recounts some theories of stone affliction: "*The affections of the kidneys are very painful, but it is very difficult to locate the real affected place, because it adheres to the external parts, and the larger intestine—which the Greeks call "kôlon"—impends over the kidneys*" [3]. He goes on to recount the causes

of calculus of which there are four: "*the efficient, the material, the instrumental and the final cause. And it is not hard to induce from the external phenomena that the concretion of a stone is due to either to cold, or to heat, as happen in rivulets and runnels when heat is generated by the fact that matter has not been evaporated and aired: in fact, when water stagnates in a runnel, there is an unnatural heat increase, which dispels all the finest parts of such muddy water while the coarse parts settle into the earth and adhere to the stony natter of the runnel, where they petrify*" [3]. These complex notions of internal heat and formation of concretions from the disruption of the balance of the four humors would virtually continue unaltered through much of the Middle Ages.

The introduction of Hermetic tradition and the questioning of the authority of particularly Galenic thought in medicine would fall upon an eccentric early Renaissance physician and alchemist, Paracelsus. He would introduce the alchemic or proto-chemical notions that stones were produced from precipitation of ingested matter. This gave the iatrochemists the advantage of providing more natural methods of cure and prevention. Chemistry held the potential solution for investigating stone disease as well as holding the secrets for their cure. The Flemish physician/chemist largely took much of Paracelsus and expanded upon these notions, Jan van Helmont. Both of these heretical physicians developed widespread following after their deaths, and their writings were widely sought after, particularly from the evolving group of surgeons/apothecaries looking for a niche not already taken by the physicians. Into this milieu also arose charlatans and quacks that peddled nostrums in public places and hawked bizarre cure-alls. The most lauded of these was Joanna Stephens of London who claimed more than a few notable individuals cured by her mysterious concoctions. Into this climate the first serious attempts to understand stone disease arose by beginning to investigate the chemical properties of the stones themselves. Reverend Stephen Hales was the father of stone chemists. He began to investigate the chemical properties of bladder



stones and Mrs. Stephens' claims. Others would follow in his wake, and within less than 50 years, the chemical identity of the five most common types of urolithiasis would be identified.

The lithology or understanding the cause of stone formation would take more sophisticated measures. In 1628 William Harvey published one the most significant works in medical history on the circulation of blood. Harvey presented his work of years of studying living physiology. His findings would trigger another sentinel figure in the progress of lithology, a now little-known physician named Johan (or Johanne) van Beverwijck to propose a new model of stone formation, in fact forming a bridge between the ancient ideas to the more modern. The father of modern surgical research John Hunter pursued the understanding of stone formation like most every other area of biology. Soon thereafter others, like Rainey, Bence Jones, and Ord, would continue the basic physical chemistry process and identify that macromolecules were needed to make crystal systems work. The other notable risk factors, obstruction and infection, would have to await the autopsy findings of stone sufferers and the pioneering work of Louis Pasteur for the foundations of microbiology. Koch invented culture techniques, and the implications of *Proteus* infections would follow in the nineteenth century.

With the rise of surgery in the nineteenth century, careful evaluation of stones in human patient kidneys was possible. J. Swift Joly at the St. Peter's Hospital for Stone noted an unusual predilection for stone to form in the lower pole of the kidneys in nephrolithiasis patients. Fuller Albright in America began a systematic investigation into metabolic problems using advanced chemistry evaluation of urine and serum from stone patients, especially those with hyperparathyroid disease. Alexander Randall in Philadelphia also proposed two new models of initiation of stone formation: type I plaques on the papillae and type II plugs in the papillae of patients lead to the formation of stone formation.

Technology was rapidly impinging upon the practice of medicine, within less than 1 year from

the evening of November 8, 1895, or the night that William Conrad Röntgen discovered X-rays the whole notion of urolithiasis and its management was about to change. No longer would patients have to be sounded for bladder stones, no longer would nephrolithiasis be the mystery that Galen alluded to previously. Physicians had an unbelievably powerful new tool for diagnosis and eventually for treatment of urolithiasis. Other technologies were introduced just prior to X-rays, anesthetic gases, local anesthetics, and finally Lord Lister's method of aseptic surgery. Each of these would evolve independently into larger, more complex technologies, but each affected the other promoting even more extensive modifications that could not have proceeded without the benefits of the other, a sort of law of accelerating returns. X-rays showed large renal stones that could not have been treated in an earlier time if the surgeons did not have general anesthesia and the patients would not have submitted to the surgery if they suffered horrible postoperative infections.

But the basic science of stone formation was not lost either; it flourished with the new notions of Fuller Albright and Alexander Randall, and others developed animal models of stone formation. Animal models led to cell culture models and finally intracellular models that could be explored with electron microscopes. Detailed micro-X-ray evaluation of Randall's plaque led to the notion of Anderson-Carr-Randall's progression of stone formation. Physical chemistry studies on crystallization involved advanced physics and mathematics for the notions of supersaturation, metastable limits, solubility products, inhibitors, promoters, and waves of precipitation. Now the history comes full circle with intense scientific interest in complex interaction of cell physiology, biochemistry, and physical chemistry in the renal tubules and the interactions forming Randall's plaques. This we will call the modern synthesis in deference to the historical significance this term is used in the history of biology to describe the fusion of evolutionary biology with genetics. In fact, this is also occurring in modern urolithiasis science as well.

## Stone Research Centers

The investigation of urolithiasis has also followed a historical discernable pattern, much like the history of medicine itself. The original separation of the craft of the physician from the religious overtones that preceded it occurred on the tiny island of Cos by the Hippocratic School. This was carried on at the Hellenistic center of Alexandria, where Galen himself was trained as a physician. The Roman era utilized much of the Hellenistic trained physicians, which became sequestered in the Byzantine Empire and the Middle Eastern cultures throughout the Dark Ages. But the beginnings of scholarship were lit again in Salerno and small centers of surgical education arose by the ninth and tenth centuries. The schools at Bologna, Padua, Montpellier, and Paris were to become the epicenters of medical knowledge. Padua produced the first real research center in anatomy sparked by the brilliant work of the Flemish anatomist, Andreas Vesalius. Anatomy sparked the surgeons to understand the human body, which sparked interest in physiology of Harvey who trained at Padua. The University of Leiden in the Netherlands became the new center for medicine with the rise of Herman Boerhaave. Stone disease was rekindled here by Rau's clarification of the surgical approach of Frère Jacques. The torch of knowledge was passed from Leiden to Paris and to Edinburgh and finally to London. Cheselden took the lead in stone surgery and perfected the perineal lithotomy, but a small school of lithotomists quietly outperformed all other centers in technique and keeping accurate data regarding every stone patient, the Norwalk and Norwich Hospital. But Civiale in Paris began to perform minimally invasive stone destructions, and the patient's benefitted. Henry Thompson learned from Civiale and brought the technique of lithotritry to new methods into widespread until an American surgeon, Bigelow utilized both the newly acquired anesthesia and the time to evacuate all of the stone fragments in a single sitting the new standard.

Stone research had been established at Guy's Hospital with the work of William Hyde

Wollaston (who did not remain there) and Alexander Marcet his pupil and collaborator. William Prout, John Bostock, Golding Bird, and George Owen Rees rounded out the first superstars of urolithiasis research at this early amazing center. Synchronously and almost isolated because these were war years, the French school of urolithiasis research had begun with Antoine Lavoisier whose protégé was Antoine Fourcroy (later to testify against him prior to his death by Dr. Guillotine's humane method of corporal punishment). Nicholas Louis Vauquelin and Joseph L. Gay-Lussac added to the mix and began an equally productive collaborative effort at the French Académie. It appears that Alexander Marcet was the only one who could significantly cross-fertilize with the French, although the Swedish Jons Jacob Berzelius also was capable of getting information to both the English and the French. Henry Bence Jones took stone disease and research to St. George's Hospital while George Rainey, William Ord, and Samuel G. Shattock continued the work at St Thomas's Hospital.

In America the first centers interested in stone disease were the Massachusetts General Hospital and Harvard University. Following in the wake of Bigelow, Fuller Albright set up a metabolic center similar to that of Richard Bright at Guy's. Albright was in charge but brought in chemists, internists, and urologists. J. Dellinger Barney developed the stone clinic. Drs. Richard Chute and Sylvester B. Kelley were the first assistants. The work continued with the involvement of a urologist, Howard Ingram Suby, who worked in the lab to develop solutions to dissolve stones. His unit, ward D, was a 10-bed inpatient unit where they proceeded to redefine the metabolism of urolithiasis. The Johns Hopkins unit also had eyes on urolithiasis. The urology unit led by Hugh H. Young also developed substantive output including pioneering X-ray diagnosis, endoscopic methods for urinary intervention, as well as basic science. In addition, one of the early residents was Alexander Randall who would go on to rival Fuller Albright in the basic understanding of urolithiasis. Randall would leave to become the head of urology at Penn. Hopkins also had



Howard Kelly and Max Brödel who contributed to urolithiasis from the Department of Gynecology. The Mayo Clinic also began its rise as a stone research epicenter. Here urologic surgery would combine with medical specialists interested in solving basic problems in stone disease. The University of Chicago also became an epicenter location led by C.W. Vermeulen and Ed Lyons; a whole host of young physicians were trained here to go on to other places, like Birdwell Finlayson. William H. Boyce also developed a stone research center at Bowman Gray School of Medicine. These were the early modern centers that bring us up to the current research centers.

Alan Rodgers developed a modern stone research program at the University of South Africa in Cape Town. Rosemary Ryall did the same at Flinders University in Adelaide, Australia. The University of Massachusetts was such a center lead by Dr. Mani Menon. Birdwell Finlayson started the stone research unit at the University of Florida that continues to perform outstanding basic science stone research. Marshall Stoller also heads up a stone research group at the University of California, San Francisco. The Mayo Clinic, the Cleveland Clinic, and the University of Chicago have all held on to the legacies started at the beginning of the twentieth century. Charlie Pak started a bone-mineral metabolic unit with an interest in stone disease that grew into a large multifaceted stone research center at the University of Texas, Southwestern that included Glenn Preminger who is now at Duke University. Jim Lingeman and Andy Evan lead a new group at the International Kidney Stone Institute in Indianapolis.

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## Renal Anatomy and Physiology

So the focus on stone disease passed quietly from the bladder to the kidney, as it should have. By the beginning of the twentieth century, the incidence of upper tract stones, nephrolithiasis, had begun to dwarf that of bladder stones. For four centuries however those who studied stones had begun to hypothesize that they were formed in the kidney. They lacked the tools to further investigate

the renal mechanisms, but this rapidly changed with the availability of quality microscopes, tissue stains, and progressive knowledge arising from the study at autopsy. Marcello Malpighi published his *De Renibus* in 1666. He noted, “*Do not stop to question whether these ideas are new or old, but ask, more properly, whether they harmonize with Nature. And be assured of this one thing, that I never reached my idea of the structure of the kidney by the aid of books, but by the long, patient, and varied use of the microscope. I have gotten the rest by the deductions of reason, slowly, and with an open mind, as is my custom.*”

The Parisian lithotomist who came to visit William Cheselden and relearn the method of perineal lithotomy first introduced by Frère Jacques returned to his homeland and developed one of the first animal models of stone disease in the black rat. The Germans led the way shown by Claude Bernard in the physiology of stone formation. Oscar Minkowski led the pack to stone formation. Wilhelm Ebstein and Arthur Nicolaier followed with numerous studies on induced stone formation in rodents. American research centers followed with the Mayo Clinic, the Cleveland Clinic, and the University of Chicago producing significant studies in the early modern era. Physiology had caught up with anatomical research. The ability to culture cells outside of the living body would further the cellular physiology into the modern era. But another field, closely allied to stone formation was crystal science research. John Duns Scotus believed that crystals grew like plants and believe like Plato had millennia earlier that they represented ideal shapes. The great Nicholas Steno noted that minerals grew by precipitation of minerals from water and noted that the angles of the regular faces were always the same. René Just Haüy revolutionized crystal science measuring internal angles and crystal growth and developed the concept of the integral molecules that make up the lattice. William Hyde Wollaston of the founding fathers of stone chemistry fame also deserves special consideration on his studies of crystals. His goniometer for measuring crystal angles is essentially still used by crystallographers today. X-ray diffraction patterns were discovered by

Max von Lau and coworkers in Munich and became utilized for atomic arrangements in 1914 by the physicists William Henry and William Lawrence Bragg. Finally, Raphael Eduard Liesegang a photographic chemist noted peculiar patterns of colloidal silver solutions and did the work on periodic precipitation of supersaturated solutions. Each of these basic scientific observations were quickly brought to medicine and stone research in particular and confirmed in urolithiasis.

As urine becomes supersaturated with mineral components, usually cations and anions, which are filtered by the glomerulus, then the risk for precipitation especially in the distal tubules increases. The physics of this process are now well known, and the physical chemistry that drives this process is also well described. John Hunter was one of the first to speculate that the process was similar to that occurring in bone and teeth. George Rainey however took this forward with substantially complex microscopic observations of crystal and macromolecule interactions in the formation of shells and uroliths. He could reproduce all of the physical chemistry that the crystallographers had observed including periodic precipitation. William Ord would take Rainey's observation even further and found evidence that his models of stone formation could be observed in carefully dissected stones from human patients. The work of macromolecules would be ultimately taken up by Bill Boyce at Bowman Gray and by Rosemary Ryall in Adelaide, Australia.

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## **Stones: A Big Problem**

Stone disease has long plagued mankind; however, prior to the Industrial Revolution the bladder was the primary repository of these concretions. In the USA and most developed countries, upper tract stones predominate (97 % in the calyx, pelvis, and ureter vs. 3 % in bladder or urethra). The incidence of stone disease has been estimated at 0.1–0.3 % or 240,000–720,000 people in the USA yearly. Urolithiasis accounts for 7–10 of every 1,000 hospital admissions in

the USA and has an annual incidence of 7–21 cases per 10,000 persons. The prevalence of stone disease is 5–12 %, or essentially 12–24 million Americans will develop a stone in his or her lifetime (this is conservative). It had been classically known that 80 % of patients with stones are males, and the onset of disease is during the most productive years (age 30–40). There is mounting data to suggest that this gender difference in stone disease incidence is decreasing further supporting a rapid expansion of new cases within the USA.

There are numerous studies evaluating local/regional variations in stone prevalence. Some possible reasons for this variability are genetic, environmental, nutritional, and occupational variables that could explain different rates of stone disease. Israel ranked first in the world as the highest incident population with stones, and the USA is 17th. These international statistics however are also changing, and the US prevalence might well be in the top five currently. Within the USA trends for higher stone incidence exist in the East versus the West. The same increased risk is noted for the South versus the North. The southeastern region of the USA has long been known to be the “stone belt” of this country. Using the southeast as the comparison region, a decreased risk of having a kidney stone was found from 13 % lower in the Mid-Atlantic region and 31 % lower in the northwest. This geographic variability has been evaluated to assess whether race, age, education, body mass, or diet affects the frequency data, but ambient temperature and sunlight levels remain the greatest risks. These geographic demographics are also changing, and the stone belt in the USA might just be the entire South, from the East coast to the West Coast, but tendrils are also extending northward.

African Americans have about a third to a quarter the incidence of stones as their white counterparts; however, they demonstrate a higher infectious stone rate. Given the fact that approximately 12 % of all individuals will experience calculus disease in their lifetime, urolithiasis represents a considerable factor in terms of the healthcare dollars spent on its management and

also the cost to society as a result of working days and wage lost.

The extent which stone formers should undergo more extensive evaluation depends upon the severity of their disease. All stone-forming patients should be made aware of the risk for recurrence. Recurrence rates vary widely from 25 % to 75 % over time. A second stone is probable in 50 % of patients by 8 years post first stone episode. Another way of presenting this to a patient is a 7 % risk of recurrence per year after the first stone passage. This suggests that stone-forming activity does not wane with time. The average rate of new stone formation in patients who have previously formed stones is about one stone every 2 or 3 years if untreated.

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