Michael E. Moran

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A Comprehensive History

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To the women who have stood with me through all trials
and tribulations of life: Gail, Mattison, and Aubrey.
To my mentors who have greatly influenced my professional
pathway—particularly Sakti Das and George Drach.
Finally, to all of the students who have endeavored
to persevere my exotic methods—"serva me, servabo!"

"Toruruwai"—MEM

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A History of Histories

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Introduction

> "*Chronology so the saying goes, is the last refuge of the feeble-minded and the only resort for historians.*" [1]
>
> —Ellis

A treatise on the varied, long, and substantive history of stone disease is essential in that it highlights mankind's sordid and repeated suffering from this particularly painful malady. Is a history of this absolutely fascinating disease really necessary? R.G. Collingwood in his classic book on history tried to answer a fundamental question regarding the importance of history; is history an art or a science? [2] Many a philosopher has debated or commented upon the role of history in mankind's development. In fact, a historian's craft has consciously affected our appreciation and interpretation of past events, so historians hold undue sway over our knowledge and appreciation of past persons and their legacy. John Burrow relates that at the very beginnings of recorded histories that Thucydides sneered at his peer, Herodotus, implying that he was overly concerned with entertainment rather than relating the truth [3]. It is to Professor Burrow that the title is derived. So here we are, presented with the classic dilemma, science or art, truth or entertainment. Stone disease has such a fascinating and long complex history that both might be attainable. There have been many histories of stone disease, and one could rightfully wonder why there is any pressing need for another. But the histories tend to be superficial, and they have a marked tendency to gloss over truly important steps along the pathway of our understanding of this complex disease. Kidney stones are in fact not just a simple disorder, but represent a whole spectrum of overlapping pathologic conditions. Even today there are intelligent clinicians that do not understand the subtle nuances of these complex processes. In fact, there are some out there that defer therapeutic modalities that truly will help those suffering from recurrent bouts of this preventable affliction. In addition, there are societies and organizations that exist to potentiate and diffuse knowledge of these varied disorders. These groups can have such appropriate names as the R.O.C.K. Society (Research on Calculous Kinetics) and have led efforts to advance the science behind kidney stone formation. Yet, even such esteemed colleagues do not often pay tribute to the Muses, and historical topics at their meetings are few and far between.

Why History?

Stone disease still represents a common affliction that about 1/6 or about 17 % of any given population will encounter. Stones represent one of the most excruciating forms of suffering that humans can encounter. In comparison to childbirth, which has always been used as one of pain's yardsticks, stone disease suffering, called colic, has typically been rated more severe! So sufferers really do have something to complain about, and the

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patients with stones have left a lasting legacy of suffering that is compelling.

In many chapters of both medical and surgical textbooks that deal with urolithiasis, stone disease in the urinary tract, there are often inaccurate representations of historical works on stones. Even the lauded “Hippocratic Oath” is used as a method of distinguishing practitioners of the art of lithotomy, those who cut on the stone [4]. This specialty has evolved into my particular specialty of medical practice, urology. Yet, this is perhaps reaching for meaning that do not actually apply to the Oath’s original intention, and the Oath’s origin itself is most certainly in doubt [5]. Into all of these muddled assertions, many believe that that the first stones occurred in historic times, since it is these times that we have written evidence. But that too is no longer the case, as paleopathology has been able to deliver to our doors individuals who have suffered in our prehistoric past. Also epidemiologists cling to the claims that stone disease is predominately a sexist condition, making the males of our species suffer more so than their female cohorts. This too is no longer true. Equal rights indeed have accrued for our sisters, mothers, wives, and daughters in most modern Western societies as stone incidence has approached parity.

All told, the saga of kidney stone disease parallels the advancement of human’s civilization, presenting a fascinating picture of medicine and surgery throughout recorded history.

A History of Stone Disease

Histories allow specialist and generalists alike to explore a topic from a unique perspective, the past. This puts knowledge and events into a perspective. It allows one to better focus upon a pathway of attaining knowledge when a particular disease, kidney stone in this instance, is complex. Timelines follow in a readily acceptable manner, and highlighting specific periods historically allows a story to develop. By separating historical periods in this fashion, we follow a historical pathway that was subscribed by the very first historians—Herodotus and Thucydides. Also some of our very first chroniclers of medicine, Plato and Aristotle, utilized this historical method with some degree of success.

Our earliest histories suffer from incomplete knowledge about exactly what our predecessors actually said, since much of early medical writing has been lost. We rely upon classicist scholarly interpretation of fragments of our former literary legacy, since invaluable repositories of learning were damaged during the millennia of human hostility that resulted in destruction of ancient libraries and museums. Yet classic knowledge of ancient Greek, Roman, and Far and Middle Eastern knowledge of stone disease had been recorded and will be presented. The fall of classic scholarship and the subsequent Dark Ages (a Western phenomenon—not in the Ottoman Empire) also affected stone disease and the medical understanding and treatment. The Renaissance followed with the maturation of some of the classic teachings maintained in the Islamic Centers of learning as well as those singular Greek holdouts in Constantinople, Andalusia, Spain, and southern Italy.

Finally scholarly, humanistic investigations of kidney stone disease would follow the reawakening of medical science. Triggered by the rise of the anatomists at Padua and Andreas Vesalius’ (1578–1657) publication in 1543 of *De humani corporis fabrica* (On the structure of the human body) [6] to his fellow Paduan disciple William Harvey’s (1578–1657) 1628 physiologic masterpiece, *Exercitatio anatomica de motu cordis et sanguinis in animalibus* (An anatomical exercise on the motion of the heart and blood in living beings) [7], knowledge about stone disease was on the brink of modernism.

Modernism and Urolithiasis

Much about the way we think about kidney stone disease is based upon the primordial thoughts of the “founding fathers” of stone disease. The beginnings of mankind’s slumber through the Dark Ages and following the Renaissance of classicism, a gifted cohort of medical thinkers began to refocus upon the subject of urinary tract stone disease (urolithiasis). Literary interests and the sufferings of patients began at the dawn of modern medicine. Sufferers such as Michel Montaigne and Desiderius Erasmus of Rotterdam wrote of the epic struggles of suffering colic as medicine strove to evolve out the Dark Ages. Johan van Beverwijck published a little heralded treatise on stone disease then incorporated the revolutionary ideas of William Harvey as to the physiology of stone development. The Reverend Stephen Hales began the chemistry of stone composition as the English government approved £5,000 for Joanna Stephens' cure for bladder stones. Finally, Carl Wilhelm Scheele and William Hyde Wollaston literally ignited the flame that would develop into clinical chemistry and the rise of both an English and French school for investigation of calculus disease from the seventeenth to the nineteenth centuries. Surgeons began to become interested in the outcomes of their surgeries for bladder stones, and itinerant lithotomists developed into hospital-based stone surgeons. In fact, hospitals based upon stone disease began, and the study of stone disease rapidly evolved. Less invasive surgeries with better patient outcomes were controversially introduced by Civiale in France and Bigelow in the United States. Radiology and the use of X-rays brought the "lurking menace" of stones into the light of everyday diagnosis. All but the radiolucent purine-based stones and the much rarer drug-type stones could now be seen and plans for therapy offered to the stone patient. In fact, the imaging modalities would themselves evolve and trigger an even more thorough investigation of the pathophysiology of the multiple types of urolithiasis. Stone disease though officially an orphan disease based upon US federal funding for research has generated a dedicated and gifted group in the twentieth century dedicated to all aspects of these disease processes. The R.O.C.K. Society is one such organization that presents research work on all aspects of stone disease in an open, highly cross-fertilized forum that includes work from Ph.D. physiologists, pathologists, endocrinologists, nephrologists, geneticists, urologists, physicists, and even engineers.

Perhaps, finally on the precipice of the twenty-first century, we might be able to rededicate ourselves to the Oath of Hippocrates by eliminating the suffering of patients with the ancient malady of urolithiasis [8]. The industrial concept of minimizing error, preventing unintended consequences of therapeutic side effects, and minimizing surgical complications can all be lumped into the notion of six sigma. This is the concept that stone patients can achieve the very best of modern medicine and live their lives with no unintended consequences, stone disease control with minimal interventions that affect the quality of life. If along the way of weaving this tale of stone diseases both historical elucidation accompanies a bit of entertainment, then so much for the science of history.

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2 Epistemology and Lithology

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 early1700s. William Cheselden dissected human cadavers and improved upon the method of perineal lithotomy. Civiale and Bigelow pioneered methods of minimally invasive lithotrity, 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

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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 lithotriptor 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 ± 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), (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)
– ***English school*** [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)], ***French school*** [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.

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 lithotrity 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 heath and disease. They believed that the impure milk could through 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 al the finest parts of such muddy water while the course 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/alchemist 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 lithotrity 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 begat 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.

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.

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 counties, 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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3 Laboring Under the Stone: A Literary Legacy of Lithiasis

Introduction

The history of mankind's suffering from disease has no more eloquent tale than that of its suffering from urolithiasis. Humans have experienced urinary colic from the beginnings of recorded civilization. In addition, our knowledge that humans have been afflicted with urinary tract stones date from an El Amrah boy, about age 16 dating from 4800 BC from Prof. G. Elliott Smith in the Hunterian Museum. This represents of scholarly review of early writings, some personal (i.e., journals), some essays, and others direct observations from eye witnesses of people suffering from urinary colic who could not do so in silence. These are explorations of written accounts of suffering from stone disease for those of us who today are still attendant upon those who suffer. This is a story of renal colic, expressed by those who have experience first hand. Attempts at expressing their suffering in their own words can provide remarkably poignant insights into those who suffer. Some such as Montaigne have left such a vast array of literature expressing their pain and suffering that it is difficult to judge which parts to include. Stone sufferers also probably had to deal with the added anxiety, that at least up until the 1920s, that the medical profession had almost nothing to offer (Laudanum was introduced for pain and suffering by Paracelsus—sixteenth century). Stone sufferers were thus doubly entrapped, lack of medical knowledge and the surgical armamentarium that was even worse—more torture than therapy.

Early Modern Suffering

"*I want to be seen here in my simple, natural, ordinary fashion, without straining or artifice, for it is myself that I portray* [1]." Thus begins Michel de Montaigne's accounts of his life and studies. Between 1577 and 1578 this extraordinary man journeyed throughout Europe to both discover himself and learn to live his life of recurrent suffering from urolithiasis. "*I am in the grips with the worst of all maladies, the most sudden, the most painful, the most mortal, and most irremedial* [1]." Montaigne traversed on horseback most of Europe and continued eloquently to document his torment, but developed stoicism, almost conversational ability to see himself outside of his body. He is an early enlightened mind that is skeptical of the medical profession of the time. He does not believe anything that has been told to him about his disease and has queried others about their medical therapies. Unfortunately, he will be forced to consult with these "*professionals*" out of sheer necessity.

Desiderius Erasmus lived between 1466 and 1536 and was widely believed to be the most brilliant mind of the age. He was a "*classic scholar*" and was recruited from almost every royal court to "*lend council*." "*This is now the fourth month*

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of my illness. First I suffered from colic, then from vomiting. This poor little body of mine does not get along very well with the doctors. All the medicines they gave me did me harm…The colic…was followed by a hard swelling which first extended all along the lower right groin. Then it centered on the pit of my stomach, almost a dragon with its teeth biting my navel while the rest of its body was writhing and its tail stretching towards my loins; when its head was fastened tight it coiled around to the left side of my navel, with its tail almost encircling it. It caused constant, sometimes unbearable pain. I could not eat or sleep or write or read." Erasmus knew almost all of the "*best*" physicians of his era and sought help from them, including Paracelsus. Though a known humanist, the suffering for Erasmus took on a darker, sinister punishing sort of experience for him, versus the more stoic descriptions of Montaigne. "*What is this [torture by the stone] but tasting of death again and again? Deliver me, if possible from his evil which is in me* [1]."

Finally, the great physician William Harvey himself suffered with stones. One eyewitness account records his suffering. "*…he made himselfe a way to putt himselfe out of his paine, by opium; not but that, had he laboured under great paines, he had been readie enough to have donne it; I doe not deny that it was not according to his principles upon certain occasions to…* [2]." The profession had nothing much to offer those suffering under the stone, not even to themselves.

Writers on Suffering

Stone disease has continued to afflict others throughout the world and writers form an interesting subject of study. Samuel Pepys kept detailed journals of his life in Elizabethan England. He religiously documented each episode of colic he suffered. "*…cold weather, which for these two days has been frost, in some pain in my bladder. Dined at home and then with my wife to the Paynter's…which brings great pain in my back…as it used to when I had the stone….* [3]." In March of 1658 he underwent the dangerous operation for the removal of a bladder stone which was about the size of a golf ball. He kept it in a special display case, and he celebrated the anniversary of surviving this ordeal with a party where the "*trophy*" was passed all around.

On September 1, 1997, this literary legacy was recapitulated by Tom Chiarella and Anita Leclerc in Esquire Magazine. "*Enter the kidney stone, the wolverine of pain, mythic in its ferocity, intensity, and blind instinct to maim. One stab of pain from a kidney stone and you'll never want to piss again. Passing one is like digesting a razor blade.* [4]" He continued in this literary vein, "*The stone can strike at any time. One minute, you're on the couch watching SportsCenter™, the next you're corkscrewing headfirst into the Berber, sucking air, waving the white flag on life. You stand up. You sit down. You curl up. You grip your sides. Nothing helps* [4]."

Finally, in the modern era when electronic entertainment has nearly replaced written medias, Kramer of "*Seinfeld*" fame summarizes his suffering from stone passage as follows: "*And this jagged shard of calcium pushes its way through the ureter into the bladder. It's forced out through the urine!* [5]"

Physicians and Suffering

The final contributions in this literary overview come from our colleagues in medicine who have suffered among the lot of the stone afflicted. Benjamin Franklin received an honorary medical degree as well as being a founding father of this country. His father and oldest brother both suffered from stones. Franklin's curiosity about this disease would portend ominously for his own future suffering. "*Because now disabled by the Stone, which the Easiest Carriage gives me Pain, wounds my bladder, and occassions me to make bloody Urine…I am more afraid of the Medicines than of the Malady.* [6]" Other great medical minds also suffered such as Antonio Scarpa, Johan van Beverwijck, Boerhaave, Thomas Linacre, John Jones, and Philip Syng Physick, but they did so silently. Thomas Sydenham though did not. "Gout produces calculus in the kidney… the patient has frequently to entertain the painful speculation as to whether gout or stone be the worst disease. Sometimes the stone, on passing…kills the patient, without waiting for the gout… [7]."

Sir William Osler likewise followed in his idol's footsteps, suffering in like fashion. His textbook of medicine, referred by many to be the bible of disease at the turn of the twentieth century, has a particular feel of empathy, since pen and patient were known sufferers. "*And then abruptly, or working out of the steady pain, came the paroxysm, like a twisting, tearing hurricaine, with its well-known radiation, followed by the vasovagal features, the pallor, cold extremities, feeble pulse, sweating, nausea, vomiting, and in two attacks, a final, not altogether unpleasant period, when unconsciousness and pain seemed wrestling for a victory reached with the help of God's own medicine – morphia.* [8]"

One final physician/author is worth presenting here, a surgeon by trade who would not best what types of descriptive metaphors might best sum up his personal agony. Richard Selzer penned "*Delicate durability describes the human body, and nowhere is this more apparent that in the urinary tract. If the liver is all bulk and thunder, the heart fist and thrust and piston, and the brain a foamy paste of insubstantial electricity, the parts of the urinary tract-namely the kidneys, ureters, and bladder- are a tracery of tubules and ducts of such fineness as would lay mad a master plumber, more, a Venetian glassblower* [9]." He warms to his topic, by introducing the reader to the pathophysiology of supersaturation. "*What is man, the son of man, asks the biochemist, but a container of salt solution in a state of more or less saturation?*" Finally he winds his way into personal torment. "*Thus is agony born. The speck hardens, concretes, is overlaid with more salt dust, becomes compressed. Spikes extend from it, pits are excavated, until it has s shape as distinctive as a face…There in the dank and humid corners of the kidney, the dragony thing lurks until weaned from its cache by the horrid principles of physics and chemistry.*" And the pain is experienced, "*Then there is Pain. But such a pain as defies words of mouth or pen to set it down, pain that, by its intensity, elects the sufferer to an aristocracy of endurance, from which all mere mortals are excluded. He who has not felt the boiling gripe of colic in back or side or belly has not the language of this elite, is illiterate of their tongue* [9]."

Discussion

Colic has been described as the most intense and severe pain that a human can appreciate. That said, it is commonly quoted that no one has ever died of pain. Stones have afflicted mankind since the alluvial beginnings. Though those of us who treat, study, investigate, and research the spectrum of urolithiasis genuinely know that these patients do indeed suffer, it is not widely appreciated to what extent. We have a priceless legacy of stone formers who have heroically suffered and written of their misery. Their legacy is a window into the patients who still suffer mostly silently, awaiting our medical wisdom, whether palliation of pain and suffering while attempting to pass these concretions or bravely harrowing the modern surgical environment of mid-infrared lasers and high energy shock waves or ultrasonic disruption.

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4 Paleolithology

Introduction

Along the alluvial savannah, mankind evolved from a hominid with two kidneys, urine supersaturated by crystals that could at any moment precipitate, forming a nidus of calcium salt or uric acid or cystine. There is currently no scientific data supporting this claim, though humans probably formed stones in all of our ancestral manifestations [1]. The growth of scientific evidence supporting man's evolutionary lineage has recently been augmented by genetic mapping. The ability to identify male lineages utilizing the "Y" chromosome and the female lineage utilizing mitochondrial DNA is widely known. In addition, there have been many successful DNA extractions from ancient bones of humans including *Homo sapiens neanderthalis* [2]. Also, paleontology, anthropology, and several other lines of investigation are keeping the frontiers of our knowledge of human evolution advancing continuously. We currently know a lot more than we ever have about our human ancestors. This new knowledge allows us to update our textbooks and come to a correct interpretation about this common human affliction.

Many chapters of urologic textbooks dealing with urolithiasis make the claim that mankind always suffered from these concretions with cryptic illusions, without any data supporting these debates [1]. Yet, there is some data relating to these contentions and looking to the wealth of paleopathologic research that in fact has been directed at ancient man, and what is known about stone disease allows one to make statements regarding the occurrence of this ancient form of disease. As of this writing, there are no definite identified Paleolithic renal or bladder stones. There are however, Mesolithic and Neolithic stones, and this is a discussion of what is known about the earliest identified uroliths, both renal and vesical.

There is some data relating to these contentions and looking to the wealth of paleopathologic research that in fact has been directed at ancient man and what is known about stone disease. That man, through speciation has or had suffered from urinary stone disease, and that suffering might well have manifested itself clinically with renal colic akin to those of other quadrupeds might be speculated. The ability of paleopathology to investigate our ancient human ancestors is beginning to demonstrate remarkable forensic information about ancient hominids. Stone disease has aroused significant research interest in this field. This is a review of that literature, with specific attention on the actual incidence of this disease.

Findings of Prehistoric Urolithiasis

Physicians have an early and significant legacy to anthropology and paleopathology with Dubois and Dart representing dramatic sentinel examples. As of this writing, there are no definite identified Paleolithic renal or bladder stones.

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Table 4.1 Listing of the most ancient stones in humans

#	Date	Location	Bladder(B)/kidney(K)	References
1	8500 BCE	Sicily	B	Piperno (1976)
2	3500 BCE	Egypt	B	Shattock (1905)
3	3500 BCE	Egypt	B	Ruffer (1910)
4	3300 BCE	Kentucky	B,B,K	Smith (1948)
5	3100 BCE	Egypt	K	Bitschai (1952)
6	2800 BCE	Egypt	K	Shattock (1905)
7	2100 BCE	France	B	Doday (1980)
8	2000–700 BCE	England	B	Mortimer (1905)
9	1500 BCE	Illinois	K	Beck and Mulvaney (1966)
10	1000 BCE	Egypt	B	Smith and Dawson (1924)
11	1000 BCE	Egypt	K	Gray (1966)
12	1000 BCE	Sudan	B	Brothwell (1967)
13	550 BCE	Italy	K	Catalano and Passarello (1988)
14	100 BCE	Italy	B	DiTota (1992)
15	100 BCE	Arizona	B	Williams (1926)
16	0–200 CE	Sinai	K	Basset (1982)

From the earliest Mesolithic female to about year "0." Modified from Steinbock [13–15]

There are Mesolithic and Neolithic stones, and this is a discussion of what is known about the earliest hominid uroliths, both renal and vesical. These terms for the historical periods of mankind's prehistoric origins were derived closely following Darwin's *On the Origins of Species* just over 150 years ago [3, 4]. A great deal of information is available on the Paleolithic diet. In addition, the one remaining artifact that has been scrutinized significantly is our ancient ancestor's bones and teeth. A remarkable volume of literature exists discussing the diet of prehistoric man/woman. In addition, there are known osseous changes secondary to parathyroid disease. The purine load in these hunter-gatherers would certainly predispose to both uric acid and calcium oxalate stone formation.

Actual stones have occurred in the prehistoric times [5–9]. The following is a list of Neolithic and Mesolithic *Homo sapiens sapiens* who lived, died, fossilized, or were preserved in some fashion with their genitourinary concretions (Table 4.1). This discussion will give the paleopathologic interpretation of their gender, age, the carbon-dated antiquity, and presumed source of origin of these stones.

The oldest known stone sufferer currently is a woman about 8,500 years ago. She was a Mesolithic cave dweller who had a predominately calcium-containing bladder stone. There currently are no known Paleolithic stone sufferers, and no other hominids have been found with a calculus. Stone disease has been found in ancient *Homo sapiens* in both the kidney and bladder about equally. In addition, stones have been found in ancient humans on four continents. Both male and female stone disease has been identified in our early *Homo* relatives. The first writings from Mesopotamia, Egypt, and India all mention stone disease indicating a truly ancient disease [10].

Humans evolved from our primate cousins about 5 million years ago. The first exodus out of Africa by a hominid occurred about 1.75 million years ago [11]. The lower Paleolithic age is typically given to run from 300,000 to 70,000 BCE (before current era), the middle Paleolithic age ranged from 70,000 to 12,000 BCE, the upper Paleolithic from 35,000 to 12,000 BCE, the Mesolithic from 12,000 to 10,000 BCE, and the Neolithic from 10,000 to 4,500 BCE. The remainder of the Holocene can be classified as the Chalcolithic or Copper Stone Age from 4,500 to 3,000 BCE and Bronze Age from 3,000 to 1,200 BCE (Table 4.2). During much of this time, humans evolved continuously, and the dietary

Table 4.2 The ages of man with aspects of their societal structure

Age	Period	Climate	Culture	Species	Economy	Dwelling
Stone	Paleolithic (2.6 million till 10,000 years BCE)	More cold than temperate	Oldowan and Acheulean	*H. habilis* *H. erectus*[a]	Hunter Gathering	Mobile, caves
		Mostly cold	Mousterian	*H. sapiens neanderthalensis*		
		Mostly cold	Chatelperronian	*H. sapiens neanderthalensis* *H. sapiens sapiens*		
		Warming interglacial	Aurignacian	*H. sapiens neanderthalensis* *H. sapiens sapiens*	Hunter Gathering Fishing First art	
		Warming interglacial	Gravettian	*H. sapiens neanderthalensis* *H. sapiens sapiens*	Hunter[b] Gathering Fishing Religion	
		Mostly cold	Solutrean	*H. sapiens sapiens*	Hunter (nets) Gathering Fishing Religion Dogs	Mobile, caves, small communities
		Rewarming following last glacial maximum	Magdalenian		Hunter (nets) Gathering Fishing Religion Trade	Mobile, caves (religious), villages
	Mesolithic (10,000–6,000 years BCE)	More temperate			Microlith tools, first wars, pottery	First complex settlements, longhouses
	Neolithic (7,000–2,500 years BCE)	More temperate			Rise of cultivation, domestication	Rise of cities

Stone disease is directly related to diet, activity, and climate
[a]One type of *H. erectus* called *H. floresiensis*, or the hobbits that may have persisted in isolation up until about 12,000 years before present [17]
[b]Large animal hunting

habits changed from locale to locale just as the ambient temperatures changed with glaciations and interglacial periods. Since stone disease is a function of both diet and climate, disease incidence might be expected to rise and fall based upon these patterns. Much information regarding the diets of ancient humans and the climates of these times is now well known [12]. Figure 4.1 represents the temperature extremes for the 40,000 years covered in this review of ancient stone disease. Interglacial temperatures were significantly higher than the glacial periods. The last glacial maximum was only about 20,000 years before the present, and the planet has been warming ever since. This should correlate with a rising incidence of urolithiasis. We know that, anatomically speaking, the primitive *Homo sapiens* was virtually identical to the present version [11]. Genetically, however, that is definitely not the case [2]. Lactose tolerance, for instance, was only introduced into our species about 5,000 years ago. Also, the height of humans was gradually decreasing up until recently (about the beginning of the Industrial Revolution).

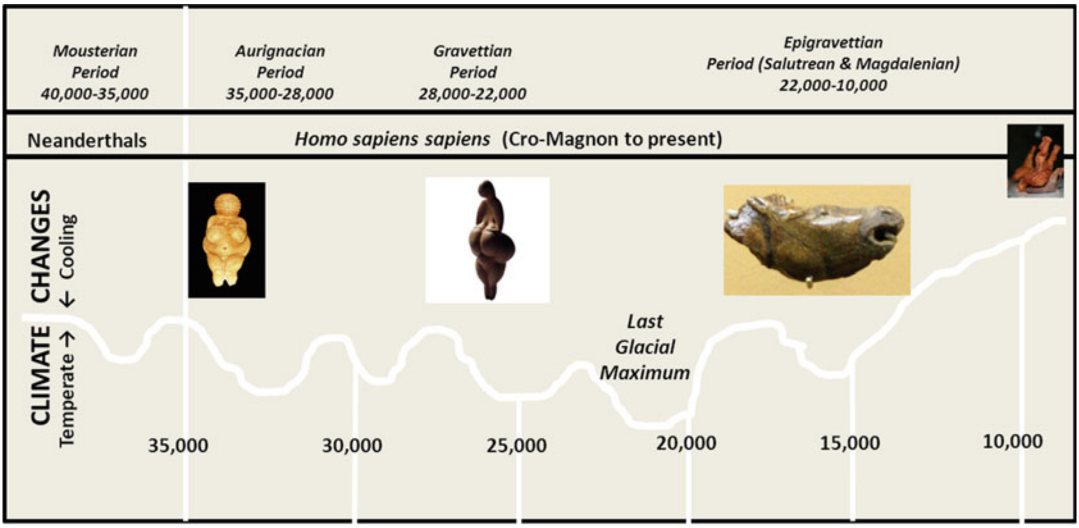

Fig. 4.1 This is a graphic representation of the maximal glacial cooling periods with the interglacial warming times. Depicted are the human periods that correspond. Evidence exists correlating global warming trends with rising stone disease incidence. Homo relatives might, therefore, be expected to have stone disease trends similar to early modern subspecies

Discussion

Stone disease has certainly affected humanity in prehistoric times. There is good evidence that stones have occurred in Mesolithic *Homo sapiens sapiens*, but there is no evidence yet of Paleolithic man or woman having this disease. There is certainly evidence that Paleolithic humans have had parathyroid disease from osteopathology [14]. In addition, there is no current evidence of other hominids getting stones, but our knowledge of these relatives remains speculative. Nonetheless, the evidence that stones have occurred in ancient humans on all four of the habitable continents suggests that the disease might well have been widespread. Stones occurred in both genders, male and female. In addition, new DNA evidence suggests that melatonin mutations might have occurred because of the increased need for vitamin D metabolism [11]. Stone disease might be less common before the lightening of skin pigmentation in our ancestral cousins. The final bit of evidence comes from climactic changes that are now well documented from several different sources, demonstrating the last glacial maximum was about 20,000 years ago and that the ambient temperatures have been rising since. As Haeckel, one of the lionizers of Darwinian Theory has once incorrectly professed, "ontogeny recapitulates phylogeny" [16]. We should be careful about the hypotheses and theories that we profess, and our knowledge of stone-age stone disease is still profoundly limited. If the study of knowledge is called epistemology and the study of ancient human disease is paleopathology, then the study of ancient stone disease should rightly be referred to as paleolithology. Paleolithology should provide those of us interested in the modern management of this ancient malady a more intellectual capacity to put an evolutionary yardstick on the antiquity of this disease.

A final bit of evidence occurred in the middle of the Miocene epoch, somewhere about 11 to 16 million years ago when the enzyme, uricase began to disappear in hominids. At least three mutations of genes in humans, chimpanzees and gorillas occurred that led to its current lack in our own species [18]. The rise in serum urate was the direct consequence of this genetic drift with a corresponding rise in the less soluble urine levels. Hyperuricosuria is a fundamental attribute of human urine that increases the prevalence of uric acid stones, calcium oxalate stones, and calcium phosphate stones. Some have hypothesized that this event also correlates with the rapid increase in brain size and intellectual capacity in the hominid species [19].

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5 Greco-Roman Stone Disease

Introduction

The Greeks and their Roman usurpers have left us a written legacy of intellectual knowledge that transcends all our modern sciences [1]. In medicine, the legacies of such immortal giants as Hippocrates, Diogenes, Heraclitus, Aristotle, Herophilus, and Erasistratus represent the foundations of modern medical ethos and practice. The Roman author Celsus and physician Galen have managed to leave a written legacy that allows historians to recreate medical wisdom from others, less familiar from the literature lost from the pyres of the Library of Alexandria [1]. This represents a review of classic medical writings in order to focus attention upon the "original" Western conceptions of urolithiasis that would ultimately influence the care and management of urolithiasis for more than two centuries.

> *Life is short, art is long, opportunity fugitive, experimenting dangerous, reasoning difficult: it is necessary not only to do oneself what is right, but also to be seconded by the patient, by those who attend him, by external circumstances* [2].
>
> —Hippocrates

The Aphorisms of Hippocrates represent a wealth of information about the ancient knowledge of medicine. Much has been written about the Hippocratic doctrine and specific diseases, such as urolithiasis. Hippocrates lived and wrote during the time of Pericles and rejected superstitious beliefs and attempted to make medicine more philosophical [3]. A review of classic Greek and Roman writings via widely available English translations serves a wealth of information. The Aphorisms of Hippocrates and much of his surviving writings are available in translated form even on the Internet [2]. Other sources can be more difficult to trace, but references can be backtracked by a wide variety of medical historical textbooks dedicated to this subject. These were the sources for all of the information about Greco-Roman urolithiasis in this treatise. In addition, any modern authors are also sought to supplement the information that could be culled in this fashion and to insure that no other primary sources were missed [4].

Stone Disease and Greco-Roman Theories

Hippocrates originally describes the shape and location of the kidneys at the back of the loins with concave sides against the large blood vessels [6]. It is attributed to Hippocrates that the paired nature of the kidneys resulted in the notion that disease that affects one equally affects the other. "*The light of the right eye with some disease affected, Is apt to make the left eye similarly infected*" [2]. Both Aristotle and Plinius believe that the kidney is a lobulated structure (from knowledge of bovine anatomy) and the "portions" of the kidney could be involved with disease while the other portions cope [5]. Galen professes that

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the kidneys are "hard and firm flesh" because the great looseness of the water that runs through them should not easily effect their flesh. Aristotle believes that the kidneys are given to animals by nature in order to stiffen and preserve the blood vessels and Galen groups the kidneys with the "glands." Hippocrates also pronounces the difference between renal and bladder stones. Hippocrates, Diocles, Praxagoras, and Galen all believe the kidneys attracted watery fluid by a hidden property and leads to a risk of stone formation, which formed from dietary excess [7]. Aristotle postulates that "*all things harden either by heat which dries the dampness, or by cold, which squeezes it out*." Two Greek physicians Rufus and Aretaeus both suggest that "*slimy earthy matter*" forms stones when kidneys are too cool, especially in older people with stones.

So stones themselves have a natural hardening tendency that is influenced by heat or cold. Hippocrates goes on to hypothesize that "gravel" does not occur in the kidneys until adulthood. Children, who often suffer from bladder stones, supposedly form and grow in the bladder, growing upon a kernel, or nucleus. Galen adds, "*the tough slime hardens by the heat of the kidneys and is baked into a stone. That the fire is indeed the cause, but that it does not act by its heat alone, but by drying and hardening the substance and because of other substances which it brings along with the flames….* [8]"

Galen professes that children form stones because "they gobble their food and run, leap and play immediately after their meals resulting in the formation of thick water." Hippocrates suggests that a child becomes gravelly if it sucks bad milk and that the milk deteriorates if the nurse eats unwholesome food. Galen continues by suggesting that milk is thick and course by nature and extremely fit to produce stone [5]. And Aristotle questioned "*Why none of the animals but Man alone can become gravelly?* [5]" Galen proposes to answer this by depending upon the strength or weakness of the organ. According to Galen, this is the reason why grown people and aged persons are more often visited with stone in the bladder but children more frequently with renal stones.

Discussion

Beginning with Hippocrates, speculations regarding the pathophysiology of stone disease began in the West. Aristotle questions: "Why none of the animals but Man alone can become gravelly?" Stones are mentioned no fewer than in 24 passages of the Hippocratic dogma. Stone formation is discussed in 6 (25 %) of these aphorisms [4]. The Aristotelian perspective is maintained by Hippocrates (heat or cold). Adult versus pediatric and kidney versus bladder stones could be attributed to heat, and eventually Galen would reiterate this theme. It is also attributed to Galen for developing the theory of disease transference to a weaker organ…kidney versus bladder, for instance. Strabo reported a whole town with hot springs that hardened (further evidence of this process) [9].

Through the country of the Cicons
Flows a stream that is most strange;
He who drinks it, pays most dearly,
As it will not spare his life…
Is at once seen stark and stiffening,
Till it is as hard as marble.

The manner of "*growing the stone*" is explained by Galen; he adds, "*the tough slime hardens by the heat of the kidneys and is baked to a stone. But the fire is indeed the cause, but that it does not act by its heat alone, but by drying and hardening the substance*" [5]. Hippocrates (fourth Book of Diseases) adds that stones in young children have their origin in the milk. Red stones arise in the kidney (the color of flesh) all others from the bladder. Galen is noted to not believe this theory of the color origin of stones. Aretaeus states that "the tendency to develop stone of the kidneys is more difficult to prevent than the fecundity of the uterus" [5]. Hippocrates talks about the incidence of stones by saying "most between the ages of 14 and 42" and "women do not suffer so frequently of stone as men" [5]. Galen astutely notices that "too adipose [patient] can hardly be cured of defects in the kidneys." Plinius [2.5] concludes: "among all greatest pains which a man can suffer in his body, the trickling piss caused by stone has of old been deemed the worst" [10]. All ancient Greek and Roman physicians and philosophers had advocated preventative measures. Ovid once penned [11]:

And let the illness not come in,
But check it as it does begin
For once it has obtained firm footing,
It scorns the means for its uprooting.

After the fall of classic Greece and before the rise of the Roman Empire, there arose in Alexandria a great medical school. Herophilus of Chalcedon became the first great anatomist and surgeon (~300 BC) and named the prostate [12]. Next came Erasistratus of Chios, also interested in anatomy and physiology (310–250 BC). Neither of these great minds left any evidence of an interest in stone disease. The decline of the Alexandrian school followed the deaths of these two great physicians, but their legacy was not entirely lost. Hegetor and Apollonius survived and kept the method alive, but again nothing on urolithiasis is mentioned [12]. Asclepiades of Bithynia and Schola Medicum taught medicine in the Alexandrian method. Rufus of Ephesus studied at Alexandria in 50 AD and practiced surgery and probably performed lithotomy. Also Marinus of Tyre, Quintus, Numisianus, Satyrus, and Pelops are some further notables but sadly left no legacy regarding stone disease [12]. Galen of Pergamum (129–199) first studied medicine under Satyrus then left to study with Pelops and then Numisianus until age 28. He then became surgeon to the gladiators, and in 161 he went to Rome with Marcus Aurelius as emperor [13]. Much of his philosophy on stones has been presented in this paper, but he also had some surgical experience. Heliodorus, Antyllus, and Oribasius all followed in the footsteps of Galen, but further interest in stone disease follows medicine in general into the Dark Ages [5]. Stone disease essentially did not rise above the hypotheses of Aristotle on the cause and perhaps peaked with Hippocrates on signs, symptoms, causes, and therapeutics. Galen certainly added some further insight but fell short of the experimentalists of Alexandria three centuries before him.

The ancient writers of medicine from Greece and Rome have left a rather significant historical legacy about the topic of urolithiasis. Not only did they document the signs and symptoms caused by bladder and kidney stones, they began to postulate hypotheses about the actual causes of this disease. Hippocrates concludes that between the ages of 14 and 42 are the most risky periods of life for stones, thus becoming the first investigator to study incidence as well as pathophysiology [5]. The Hellenistic legacy of these thinkers has persisted to our current era. We no longer follow the admonition to "not cut on those suffering from the stone," but we still seek epistemological truth. The great Greek philosopher Epicurus died from complications of stone disease, and it seems fitting to end with his own words… [14].

I write to you on this happy day which is the last of my life. The obstruction of my bladder, and the internal pains, have reached the extreme point, but there is marshaled against them the delight of my mind in thinking over our talks together. Take care of Metrodorus' children in a way worthy of your lifelong devotion to me and to philosophy.—Epicurus (341–270 BC)

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6 Dark Ages, Dark Therapies

Introduction

The Dark Ages is a term used for the time in human history from the fall of the Roman Empire to the beginnings of the Renaissance. In 410 CE Alaric and his warrior fiefdoms sacked the eternal city of Rome beginning the fall of the Empire. This is often depicted as an age of stupidity, when mankind's search for knowledge and questioning nature had fallen to the lowest levels since the prehistoric era. Yet this was the time of the rise of Christianity, the development of the scholarly monastic tradition. Galen's teachings would become entrenched as the basis of educated medical practitioners. Other itinerant healthcare workers were very much in existence, including midwives and barber-surgeons. Mankind's scholarly output dwindled into nothing, but the frantic copying of hermits and monks literally defines the Middle Ages. But this is not entirely the case for history nor is an accurate depiction of these centuries of human existence.

Middle Ages for Urolithiasis

Emperor Constantine established Christianity as one of the official faiths from 313 CE. Constantinople now modern Istanbul on the Bosporus became the new bastion of the Roman Empire. Constantine moved to fortify his new capital in 324 AD, and the great Empire formally split by 364 each ruled by a separate emperor. Religion became the center of all knowledge, and "healing" and "holiness" became intertwined [1]. Hippocratic teachings and Galenic medicine held on by a thread. Luke the Evangelist was himself a physician. Christ told physicians to heal themselves and gave proofs of his divine powers through miraculous acts of healing. Miracles and the intervention by prayer and visiting shrines of saints became a flourishing industry. St. Luke and St. Michael were often called upon for all manner of illnesses [2]. Other saints however began to be called upon for specialty problems: St. Anthony for erysipelas (St. Anthony's fire), St. Sebastian for pestilence, St. Blaise for goiter and sore throats (this ritual is still performed in Catholic churches), but for kidney stones it was St. Alban [3]. St. Luke brought to stone formers one of the most trusted methods of stone prevention and cure, the "tongue stones" from the island of Malta [4]. The Church's overarching stigma of suffering simply equating to divine punishment persisted. Emperor Justinian I (527–65 CE) suffered but was miraculously cured from the holy spring of Zoophoros and simple hydration [5]. Emperor Justin II (565–578 CE) followed in his filial footsteps but suffered and died after surgical attempts at perineal lithotomy, and eventual partial penectomy failed to save his imperial life [5]. The Emperor Michael II (820–829 CE) also died of fatal bladder stones at a young age. Henry II, King of Bavaria, suffered from stones. King Henry was miraculously cured by St. Benedict, who operated on him while he slept. A famous sculpture of St. Benedict placing the stone in the

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Fig. 6.1 Sculpture by Riemenschneider of St. Benedict operating on him and laying the stone in his hand (1024)

King's sleeping hand from a sculpture by Riemenschneider in 1024 CE is shown in Fig. 6.1. Emperor John VI Cantacuzenus (1347–1354 CE) in his own words describes his bouts with renal colic. Medical therapies had virtually no effect, and his sufferings subsided on their own [5].

Charity became a cornerstone of Christian faith and early church leaders began to organize charitable institutions (Leontius of Antioch in 344 CE set up hostels, Bishop Eustathius of Sebasteia built poorhouses around 360 CE, and St. Basil constructed outside of Caesarea a house for the sick) [1]. A hospital was founded by Fabiola in 390 CE taking care of Rome's poor. St. Sampson's in Constantinople was a large hospital that had a surgical theater and segregated into male and female wards. By 650 CE the hospital had a hierarchy of physicians, teaching facilities, a special place for elderly, and leper house outside of the city's walls [1]. The Christian era of hospital building began by the thirteenth century. St. Leonard's in York had 225 sick by 1287; Milan, Siena, and Paris all had similar institutions. London's St. Bartholomew's started in 1123 and St. Thomas's started around 1215. The Hôtel Dieu next to Notre Dame had physicians on staff by 1231, and Sta. Maria Nuova in Florence (where Leonardo da Vinci first performed autopsies) was open by 1288 [1].

Another phenomenon of the late Middle Ages was the development of universities in the twelfth century. Paris was founded in 1110, Bologna in 1158, Oxford in 1167, Montpellier in 1181, Cambridge in 1209, Padua in 1222, and Naples in 1224. These universities extended the work started in Salerno and interacted with scholars from Muslim Spain, particularly Gerard of Cremona in Toledo [6]. Death was the obsession of the Dark Ages; people and populations were experiencing plagues and pestilences that had no explanation other than the wrath of God [7]. The zenith of medicine and treatment was represented in the development of the zodiac and astrology to help explain health and disease. Astronomy began to be taught in these institutions of higher learning accompanying medicine. It was important to know of the alignment of the 12 zodiac regions with a patient's birth and at key times of their lives [7].

Dark Ages

Although the Middle Ages or Dark Ages included up to the fourteenth century, not all treatments were shrouded in mystery. Early in the opening years of this century, the Dominican friar Theodoric Borgognoni of Lucca (bishop of Cervia) was interacting with Hugh of Lucca, Jean Pitard of Paris, and Lanfranc of Milan [8]. Another cleric who obtained degrees in theology, philosophy, and medicine from Montpellier and Paris was Henri de Mondeville [9]. He became a military surgeon for King Phillip in 1301 and joined the faculty at Montpellier by 1304. He developed 13 original drawings and charts to demonstrate anatomy to his students (Fig. 6.2) [10]. He practiced surgery for over 60 years and wrote his magnum opus beginning in 1306, *Chirurgie* [11]. He most likely influenced Guy de Chauliac (1300–1368) who quoted him extensively [11]. Though Henri did not write about urinary stone disease, he did comment upon the anatomy of the urinary tract and offered the sentinel notion of a one-way

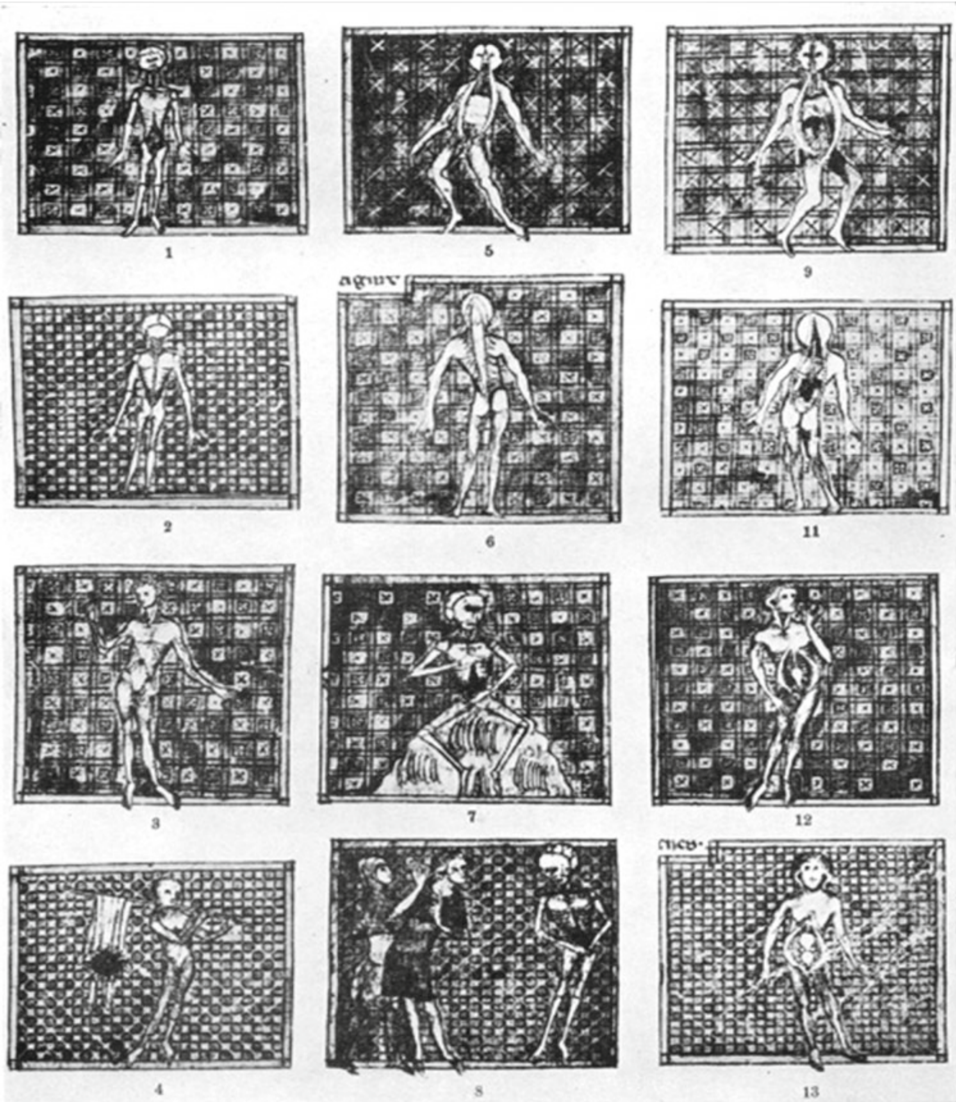

Fig. 6.2 Henri de Mondeville's writing was in Latin. There are 18 known copies of his manuscript prior to the development of the printing press. Pagel in Berlin printed the first edition in 1889 on his anatomy only. Henri's surgery was published in 1892. The first printed complete volume of de Mondeville's work was the French M. Nicaise in 1893

valve mechanism for the ureterovesical junction [12]. He also inherited and perpetuated Theodoric's belief that suppuration of wounds was not beneficial to healing following surgery [13].

Another notable surgeon who certainly also treated stone disease was Lanfranc. Guido Lanfranchi was born in Milan, became educated, and developed an interest in surgery. He fell prey to the misfortunes of war and was forced to leave Milan for Lyon and Paris where he became a popular teacher at the Collège St. Côme [14]. There he composed his magnum opus, *Chirurgia Magna*. Leonard Rosenman has recently published an English translation of the manuscript, originally written in 1295. His Treatise III, Division III, Chapter 8, is devoted to his knowledge regarding urolithiasis [15].

The *Chirurgia Magna* consisted of five treatises with subdivisions in each. Treatise III concerns specific surgical conditions. He mostly recapitulates the classic ancient writers, Galen and Hippocrates, regarding the formation of stones. Stones form from the hardening of humors. Kidneys have great natural heat which makes the stone. Children, whose kidneys are less hot, form bladder stones. Here lies, perhaps, the origin of the myth that bladder stones are white and renal stones are red. Here also, he records one of the most fascinating methods, along the lines of current theories to aid in expulsion by applying hot, split cucumbers to draw down a stone through the ureter [15].

It is hard to understand the mentality of those who practiced surgery, but Lanfranc was read widely and much quoted by subsequent authors. It appears that the myth of the white bladder stone versus the red renal stone may have started with him.

Dark Remedies

Beginning in the early Christian era, one of the more unique chapters on the treatment of urolithiasis has its beginnings. Sharks are cartilaginous fishes with calcium phosphate mineral teeth. These teeth represent some of the most common fossil remains from Mesozoic and Cenozoic deposits. Some sharks have over 300 teeth in their jaws. Fossil shark teeth have been called “glossopetrae” before the origins of these remnants of these ancient creatures were full appreciated [16]. These were called various names throughout history, linguae melitensis (Maltese tongues) and linguae S. Pauli (St. Paul’s tongues). The myth begins in about 60 CE when St. Paul became shipwrecked on the island of Malta en route to Rome. He was apparently bitten by a poisonous snake but did not become ill because of the miraculous properties of the Maltese tongue stones. The people of Malta developed a lively trade during the Middle Ages for the sale of tongue stones which were touted for relief of colic and kidney stones [17].

Oribasius (325–97) studied Galen and wrote on Galenic medicine and commentaries on Rufus of Ephesus [19]. The North African physician, Caelius Aurelianus (c. 420 CE), wrote a large Latin handbook for physicians, *De morbis acutis et chronicis* (On Acute and Chronic Diseases) [18]. A Greek physician, Alexander of Tralles (c. sixth century), wrote *Libri duodecim* (Twelve Books of Medicine) [18]. Paul of Aegina (c. 640) studied and practiced in Alexandria. His only surviving work is an encyclopedia of medicine, *Epitome medicae libri septum* (Seven Books of Medicine) [18]. But with these exceptions, the rise of Islam and the development of the Middle East usurped the knowledge of the Greeks and maintained the scholarship of medicine. But in the Dark Ages of Western Europe, the flicker of knowledge was held tenuously until the founding of the Salerno School, perhaps in 1063 CE, supposedly by a Latin teacher, a Jew, an Arab, and a Greek. The writings of Hippocrates, the school of Alexandria, and the Galenic writings with the support of Alphanus a Benedictine monk at Monte Cassino were brought back to Europe. Both Arabic and Greek texts were translated by Constantinus Africanus (c. 1020–1087 CE) and the *Pantegni* (The Whole Art), Galen’s *Method of Healing*, and Hippocrates’ *Aphorisms, Regimen in Acute Disease, Prognostic, and the Art of Medicine* were all available [18]. Finally, Constantine also translated a version of Hunayn’s (Johannitius’) *Medical Questions* which were used in teaching physicians [18]. A Salernitan physician, probably Arnald of Villanova, wrote *Regimen Sanitatis Salernitanum* (Salernitan Regime of Health) that supplied healthy tips for living. It highlighted hygiene, exercise, diet, and temperance. There are no records of outcomes, but one could little doubt that a healthy diet and liberal fluids were probably better than tongue stones and hot cucumbers in treating stone patients.

At the school of Salerno there practiced the now almost mythical teacher Trotula [19]. As Salerno developed, we know that by 1140 CE those rigid admission standards were required for studying medicine. The Regimen Sanitatis Salernitanum required specific physician behavior [20]. Women were both allowed to practice as well as teach. We have circumstantial evidence that Trotula was married to another physician, John Platearius, and that two of her sons also became physicians. She probably lived between the eleventh and twelfth centuries and wrote several treatises on medicine. One *De passionibus mulierum curandarum* (was on diseases of woman) and the other *Summula Secundum Trotulam* form the basis of her treatment of urolithiasis [21]. She used all aspects of the medical armamentarium including amulets, homeopathy, rituals, herbs, suppositories, but probably not surgery. She wrote about the medications and herbs that treated stone disease and colic. She recommended sassafras and root of grasses BID or TID. If the stone was associated with colic (ureteral), she used cook mallow, cabbage, sassafras, watercress, and nettle seeds in wine and oil. She would recommend topical applications of salt water to the flank. For bladder stones in men, she anointed the penis with oil of laurel. She mentions dietary modifications, adding sharp foods to the diets of stone sufferers but recommended cheese and lemons. She is the first to recommend "suction" to the genitals if stones were stuck in the urethra. There is no description of this method so the truly curious will have to wait to the Renaissance for a more complete description of this technique [21].

Discussion

The Dark Ages were just another time in the long evolutionary progress for understanding stone disease. The great historian, Norman F. Cantor, describes the popularity in 30-year cycles. The people were remarkably hardy, typically working long arduous labor in a highly regimented social hierarchy. Stones afflicted rich and poor alike, and much of our recorded suffering is from the royalty. But the loss of classic learning from the Greeks did little to assuage the suffering or the treatment of urolithiasis patients since their patent medicines of mummy's parts, glossopetrae, and hot cucumbers probably did nothing. Surgery also was a desperate alternative [22]. Lithotomy was performed in the method unchanged from the description of Celsus. Risks were high and morbidity was also, as seen from the complications and death of Emperor Justin II [1]. Visiting religious shrines, making votive offerings, and entreating a patron saint, such as Alban, were not so far-fetched, when bleeding, purging, and lithotomy were the alternatives.

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7 Renaissance of Urolithiasis

Introduction

The Renaissance is typically described as the time of the fifteenth through the seventeenth centuries. Again, much like the Dark Ages, it principally applies to Western Europe. Also akin to the Middle Ages, its exact beginning and ending are not written in stone (pun intended). Some might feel that the fall of Constantinople in 1455 with the influx of classic Greek works might be the emphasis for the beginning. Certainly, Christopher Columbus's voyage of discovery might also lay claim as the opening of the beginnings of questioning man's place in nature. Johann Gutenberg's experiment with movable faced type would revolutionize the production, and transmission of text could also easily be the sentinel event in the 1430s. One recent professor of Humanities from Harvard eloquently argues that a little heralded Italian book hunter, Poggio Bracciolini, was the direct cause of the Renaissance by finding a lost copy of Titus Lucretius Carus' ancient poem *De rerum natura* or *On the Nature of Things* and publishing it again for mankind's consideration [1]. Poggio stumbled upon a rare surviving copy possibly in January of 1417 in the Benedictine monastic library at Fulda. He had the 7,400 lines in Latin text written in hexameters copied and sent to him at the Vatican. He sent this sole copy off to his friend Niccolò Niccoli to transcribe it in his elegant hand. There are 50 known copies that survived from this first dissemination. Both the monastic original and the scribe's copy for Poggio no longer exist.

Why would a poem about the nature of things become so significant? Lucretius was a Roman Epicurean follower, and *De rerum* is a glorification of the teachings of Epicurus. Epicurus was born on Samos in 342 BCE to a poor Athenian school master. Epicurus was enthralled by the idea of atoms first popularized by Leucippus of Abdera and his protégé Democritus. There were many competing theories to explain the universe, but this small particle that represents the core of matter was a dazzling explanation [2]. Epicurus took to this theory like no one previously and developed an entire philosophy around the astounding implications. In his quiet garden and dwellings in Athens, Epicurus propounded in ordinary language, the universe is "atoms and void and nothing else." This is the first and most alarming fully atheistic ideology that liberates humanity from superstition, pagan beliefs, divine intervention, and every other fear that mankind had generated. There is serenity in living and dying. The purpose of life, according to Epicurus, is the free pursuit of pleasure. He did not equate pleasure with debauchery or gluttony as his enemies were wanted to espouse. He urged frugality to his students. He admired prudency, personal honor, justness, and philanthropy.

It is little wonder that a philosophy of pleasure was somewhat scandalous at the time and in the eyes of the Christian and Jewish faiths that followed. But Epicurus lived a simple quiet life, and other than a few letters and written fragments

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of his disciples, little remains from his actual writings and philosophy except in the extraordinary beautiful verses of Lucretius. But prior to leaving Epicurus, he has one tantalizing aspect that must be covered in the Renaissance of calculus disease. He died of massively painful bladder stones. He died most likely in 270 BCE at the age of 72 at his own school, called the Garden between the Stoa and the Academy. He died with prolonged colic probably with bladder stones and wrote to Idomeneus: "*I have written this letter to you on a happy day to me, which is also the last day of my life. For I have been attacked by a painful inability to urinate, and also dysentery, so violent that nothing can be added to the violence of my sufferings. But the cheerfulness of my mind, which comes from the recollection of all my philosophical contemplation, counterbalances all these afflictions. And I beg you to take care of the children of Metrodorus, in a manner worthy of the devotion shown by the young man to me, and to philosophy*" [3, 4].

Out of Darkness

With the establishment of institutions of higher learning, medicine rapidly became an intellectual endeavor. Pharmacology was linked to alchemy, and medicinal plants were sought from the New World. One Renaissance practitioner is almost emblematic for the whole period of medical history, Theophrastus Philippus Aureolus Bombastus von Hohenheim (c. 1493–1542) better known as Paracelsus (literally meaning surpassing Celsus) [5]. That he embodied the iconoclastic tradition of genius of the Renaissance is an understatement. He drastically broke with tradition, repudiated Galen, developed a chemical theory for diseases including stone disease, and became the scourge of the medical establishment [6]. Despite all of this, or perhaps in addition, he was a prolific writer with most of his works published posthumously. Stone disease became understood in terms of alchemical precipitation, which is in fact the cornerstone of modern-day supersaturation theory. In *De morbis tartareis (On Diseases of Tartar)* published in 1531, he argued that external factors such as local water supplies might produce gout and stones [7]. He gave one of the first epidemiologic observations by stating "*in Switzerland, the most healthy land, superior to Germany, Italy and France, nay all Western and Eastern Europe, there is no gout, no colic, no rheumatism and no stone.*" He went on to hypothesize that stones like the tartar forming on wine skins is transformed by "spirit of salt" into stony substances. He was the earliest proponent for the chemistry of calculus disease. In addition, this rebellious physician championed the use of narcotic pain medications using opium to establish a humane method of helping sufferers with colic [8]. Paracelsus cured the famous printer and publisher Johann Froben and came to the attention of the classic scholar of the Renaissance, Desiderius Erasmus (1466–1536). Erasmus was the world-renowned personality of his time, and undoubtedly the consultation with Paracelsus added to his reputation immensely [9]. Erasmus suffered from recurrent bouts of kidney stones and most certainly saw the young renegade physician (he was 33 at the time) at the request of his enthusiastic patron, Froben. Paracelsus was teaching medicine at the time at the university in Basel. Erasmus was skeptical regarding advice from any physician, but he was apparently pleased with his consultation with Paracelsus. Did he treat his most famous patient with his *liquor alkahest*? We do not know. Whole dissertations have been done on the ingredients of his famous stone elixir [10].

Paracelsus' most ardent disciple and next to investigate stone disease was Jan Baptista van Helmont (1579–1644). He was educated in the Netherlands at Louvain and became deeply interested in alchemy. He obtained his M.D. degree in 1599 from Louvain. He married a wealthy heiress and began to practice medicine and research "pyrotechny," alchemy. Like Paracelsus, much of his writing was also printed after his death [11]. He developed an intricate pathologic system that was clearly not following accepted Galenic teaching. Helmont believed instead that each disease was an external thing, possessing a specific morbid seed (semen) capable of attacking the body. Helmont called the aggregate of metabolic centers of the body an "archeus" or spiritual force that could be investigated. This was based upon internal chemistry. He did rather sophisticated experiments on the kidneys and renal function, measuring urine for 24 h and noted two principal salts in urine: one that was from food and one a crystalline form volatile to heat (possibly urea). Helmont followed Paracelsus in the concept that all organic processes and disease were chemical and that fermentation was the chief mechanism [12]. The idea of fermentation though is not absolutely the same as our current understanding, and he distinguished six phases to the process. He fundamentally did not treat stone patients by restoring the balance of the humors. Helmont clearly separated the sick patient from the illness. He tried to find specific chemical substances that worked. He also pursued a chemical solvent for kidney and bladder stones [13]. Robert Boyle (1621–1691) the father of English chemistry would also become interested in this quest (more on this later). Helmont might be the first to believe that a fever was not a product of humoral putrefaction, but a reaction to irritation and a natural healing process. Helmont was proud of his medical differences from the classic physicians and referred to himself as "Philosophus per ignem," a chemist [10]. As the Netherlands during this time was under Spanish rule, he eventually was condemned by the Inquisition (1625 for 27 heresies, impudent arrogance, and association with Luther), and he like Galileo was placed under lenient arrest, though forced to recant his beliefs.

Humanism and Suffering

Another specific feature of the Renaissance is the development of the notion of humanism. Humanism is equated with the rise of mankind's beliefs that via intellectual pursuits, humanity could gain knowledge and influence the time on Earth. This is quite distinct than the Medieval notions that man's time on this planet is for penitence, sacrifice, and spiritual preparation that characterized much of the Middle Ages. The humanists believed that man could better his station in life. The Renaissance gloried in man's achievements and capacities. Not all humanists would necessarily follow this renewed faith in man's ability, there was always some lingering capacity to believe in divine intervention and that medical suffering was an affliction imposed by an all-powerful God. Both scientific giants of the Renaissance, Galileo Galilei (1564–1642) and Isaac Newton (1642–1727), suffered from stone disease [14]. Both were of the stoic variety and did not look to God for redemption or relief of their suffering.

This stoicism was reflected in the writings of the French nobleman and stone sufferer Michel de Montaigne. In his treatise "*Of Experience,*" he notes that he has "*a new acquisition- the kidney stone.*" He stated in "*Children and Fathers*" that "*I am in the grips with the worst of all maladies, the most sudden, the most painful, the most mortal, and the most irremedial*" [15]. Montaigne personified his stones, taking them with him on his travels. He gave birth to them; they were his death, his companions. He boasted about his disease: "*I have fallen into the commonest ailment of men of my time of life. On all sides I see the afflicted with the same type of disease, and their society is honorable for me, since it preferably attacks the great; it is essentially noble and dignified*" [16]. Montaigne deplored the medical opinions he obtained. He loved doing the things that his physicians advised against. He found immense pleasure in long rides upon his horse; he loved red wines and great food. He did succumb to medical opinions and sets out to try mineral water cures, perhaps in Rome. By September 1580 he had taken to the road and recorded his travels in his published *Travel Journal.* He relished his description of the affect his illness had on others: "*The fear and pity that people feel for this illness is a subject of vainglory for you… There is pleasure in hearing people say about you: There indeed is strength, there indeed is fortitude! They see you sweat in agony, turn pale, turn red, tremble, vomit your very blood…discharge thick, black, and frightful urine, or have it stopped by some sharp rough stone that cruelly pricks and flays the neck of your penis; meanwhile keeping up conversation with your company with a normal countenance, jesting in the intervals with your servants, holding up your end in a sustained* *discussion, making excuses for your pain and minimizing your suffering*" [15]. Michel de Montaigne found a method of humanely dealing with his illness. He faced it and moved forward. He did not let the suffering get in the way of living: "*Here is another benefit of my illness, peculiar to it: that it almost plays its game by itself and lets me play mine, unless I lack courage; in its greatest throes I have held out for ten hours on horseback. Just bear it, you need no other regimen*" [15].

Desiderius Erasmus is perhaps nowadays overshadowed by Montaigne in philosophy and literature, but that was certainly not the case in their lifetimes. Erasmus was the sterling model of Renaissance academia and was courted by monarchs and popes for his scholarly achievements [17]. In his lifetime, Erasmus of Rotterdam's (his own attempt to hide his past) literary output was some 16 million words, about one hundred and fifty volumes. He wrote his classic *The Praise of Folly* (dedicated to his friend Thomas More) during bouts of extreme colic. Erasmus was not so stoic in his description of his bouts with colic: "*This is now the fourth month of my illness. First I suffered from colic, then from vomiting…This poor little body of mine does not get along very well with doctors. All the medicines they gave me did me harm. The colic was followed by an ulcer, or more accurately, by a hard swelling which first extended all along the lower right groin. Then it centered on the pit of my stomach, almost like a dragon with its teeth biting my navel while the rest of its body was writhing and its tail stretching towards my loins; when its head was fastened tight it coiled around to the left side of my nave, with its tail almost encircling it. It caused constant, sometimes unbearable pain. I could not eat or sleep or write or read*" [15]. Erasmus's *Adagia* was reprinted by the famous Venetian publisher Aldo Manuzio. Erasmus was then 38, and he suffered his first attacks of colic in Venice. He had developed a fondness for good wines, and it was widely believed that his drinking precipitated his bouts of stones. He as well as his physicians believed that wine was the best treatment for his illness [17]. It is fascinating that this particular work, *Adagia,* became one the pieces that would later inspire the writing style of Montaigne, fellow sufferer in stone disease.

Questioning Nature?

Another common thread of the humanists that lived during the Renaissance is the devotion to nature. The average person appears to have developed an interest in natural things. This is reflected of course in the realism of the art of such icons of the Renaissance as Botticelli, Leonardo da Vinci, Michelangelo, and Raphael (Fig. 7.1). In addition, writing, architecture (Leon Battista Alberti—Santa Maria Novella in Florence), and medicine began to reflect this rapture in the beauty of nature. Botticelli was heavily influenced by the physician-humanist Marsilio Ficino in his allegorical painting of *Primavera* (idealizes Neoplatonic thinking in a garden of earthly delights) [17]. Cervantes extolls the natural beauty in his mad knight's quest. Sir Thomas More expresses his fascination in the beauty and simplicity of nature in his description of Utopia [18]. The music of the French composer, Marin Marais (1656–1728), *Le tableau de l'operation*

Fig. 7.1 Painting of a Renaissance stone

Fig. 7.2 Marin Marais and his musical piece "*Le tableau de l'operation de la traille*"

de la traille describes the surrealism of stone disease and the horror of stone surgery. Marais was both a composer and a gifted performer on the bass viol which comes the closest to the human voice [19]. It is not known if Marais suffered from stones, or even underwent the surgery for a stone, but his musical piece certainly suggests an intimate association with the horrors of this experience (the piece can be heard online at http://le Tableau de lOperation de la Taille) (Fig. 7.2). Desmond O'Neill has described this piece as follows: "*The piece is short, as was the operation in those days- a skilled operator could perform the task in just under a minute. The course of the operation is easy to follow. Onomatopoeically there is a tremolo when the patient confronts the medical equipment; a rising diatonic scale when mounting the operating chair; descending parallel thirds when the catheter is introduced; fast and (for a viola da gamba) high pitched tremolo during the operation itself; punctuated rhythm in alternating fourths and rests finally dying away, representing the weakening flow of blood; and descending melodic movements when the patient is taken to bed. The tone structure mirrors the tension: the preparation of the operation in E minor, the preparation of the actual incision in a quasi-undulating harmony, the painful part of the operation in the subdominant A minor, and the care of the patient after the surgical treatment in a modulation back to E minor. The suite's next movement, les Rèlevailles, pictures the recovery and joy on surviving the operation, not surprising considering that nearly half of those who underwent the procedure died*" [20].

Michelangelo (1475–1564) suffered from recurrent bouts of colic, and during the painting of the ceiling of the Sistine Chapel, he had a six-month hiatus that upon returning to work he inscribed a reniform background with God separating land from water (Genesis 1:9–10) which was perhaps a metaphor for stone disease. His physician was the famous anatomist and surgeon Realdo Colombo (1516–1559), who served as assistant for Vesalius and succeeded to the chair of anatomy in 1540 [21]. He described his torture and torment via the historian of Renaissance artists Vasari: "…*in his old age he suffered from gravel in his urine which finally turned into kidney stones, and for many years he was in the hands of Master Realdo Colombo, his very close friend, who treated him with injections and looked after him carefully*" [21]. No one knows exactly what concoction that his physician prescribed. But tellingly, Michelangelo describes it in a letter from March 23, 1549: "…*having been given a certain kind of water drink, it has caused me to discharge so much thick white matter in the urine, together with some fragments of the stone, that I am much better and hope in a short time I shall be free of it- thanks to God and to some good soul*" [21]. He continued throughout that year to discuss his stony condition: "*Morning and evening for about two months I've been drinking the water from a spring about 40 miles from Rome, which breaks up the stone. It has* *done this for me and has caused me to discharge a large part of it in the urine. I have to lay in a supply at home and cannot drink or cook with anything else…*" [21]. He was typically stoic about his suffering; he disclosed tidbits in his letters, but he survived to nearly age 90.

Medicine and Surgery

The final fascination of the Renaissance that also defines this era is the return of enrapturement with Plato's philosophy and the fall of Aristotle's hold over academia. Gemistus Pletho (1355–1450) who came to Florence in 1440 and ended up staying as a guest of the Medici's brought his scholarship and original Greek works of Plato along with him. This influenced the early humanists such as Petrarch to question the scholastic musings from the Middle Ages. Newfound questions and reinterpretation of the actual writings of the Ancients became the new passion. Medicine and medical writings would also follow this path.

In 1577 Dr. George Pictor wrote a small 65-page book On the Treatment of the Renal Calculus; an English translation soon followed. In classic Renaissance fashion, Pictor starts off with an elaborate dedication to his patron Gallo Blet saying "*knowing full well that one runs the risk of being smitten with stone in the kidney at any time*" [22]. He begins with a bibliographic history of knowledge of stone disease from Galen to the present time. He states that it is easier to prevent stone disease than treat it. He discusses principles of prevention. These are as follows: air, food, drink, sleep, waking, exercise, rest, evacuation of the feces, and the condition of the mind. Each of these could be manipulated to reduce the effects of stones or to prevent them. In chapter two he goes into details about diet, especially foods that are lithogenic. He cautions people about sleep: "*Sleeping on the back overheats the kidneys, thus contributing to the formation of gravel; therefore, this position must be avoided*" [22]. This theory has not been entirely forgotten. Marshall Stoller at the University of San Francisco has recently written on stone predilection for one side or the other based upon sleep habits. He does not go so far as Pictor in speculation about heat, but pooling of blood and stasis are both hypothesized as relevant risk factors in the pathogenesis of stones in Stoller's model [23]. He believes that exercise before meals also reduces the risk, but exercise after eating should be avoided. His chapter three is regarding diagnosing stones by symptoms. He quotes Galen and Hippocratic teachings. Pictor discusses simple and compound remedies for both stones and colic. These consist of sassafras, leaves from wild poplars, parsley seeds, violets, and cathartics: "*There are also agents which disintegrate the stone, such as lithospermum, saxifrage and the eyes of crayfish*" [22].

Surgical writers increased in the Renaissance. The authors wrote about their thoughts of the profession and increasingly were read and discussed. Ambroise Parè (1510–1590) was one such writer and thinker. He revolutionized the treatment of battle injuries but did not talk much about stone disease or stone surgery [24]. Felix Würtz (1518–1575) was another little heralded surgeon also from the Renaissance whose career spanned four decades and wrote about his everyday practice. He again does not much talk about stone surgery [25]. But his near contemporary, Pierre Franco most certainly did. Much surgical writing from the Renaissance period has only recently been translated into English. The initial writings from famous surgeons have a wide breadth of details concerning surgery. One bizarre method of dealing with particularly difficult urethral stones was presented by Pierre Franco (more on this under chapter on Lithotomy) [26]. Franco would leave a legacy to later writers, such as Ambroise Paré who would quote him. Franco also might just be the first in modern times to operate suprapubically to remove a large bladder stone in a young boy. But one particular aspect of surgery promised during our discussion of Trotula in the preceding chapter bears mentioning; interestingly it was omitted from commentary by Paré.

Review of the surgical writings of Franco reveal seven chapters that deal with bladder and kidney stones, and the entire Book II regards urology in some detail. Particular attention is drawn to Chap. 27 where Franco begins to discuss passing catheters and sounds. In fact, he will describe a

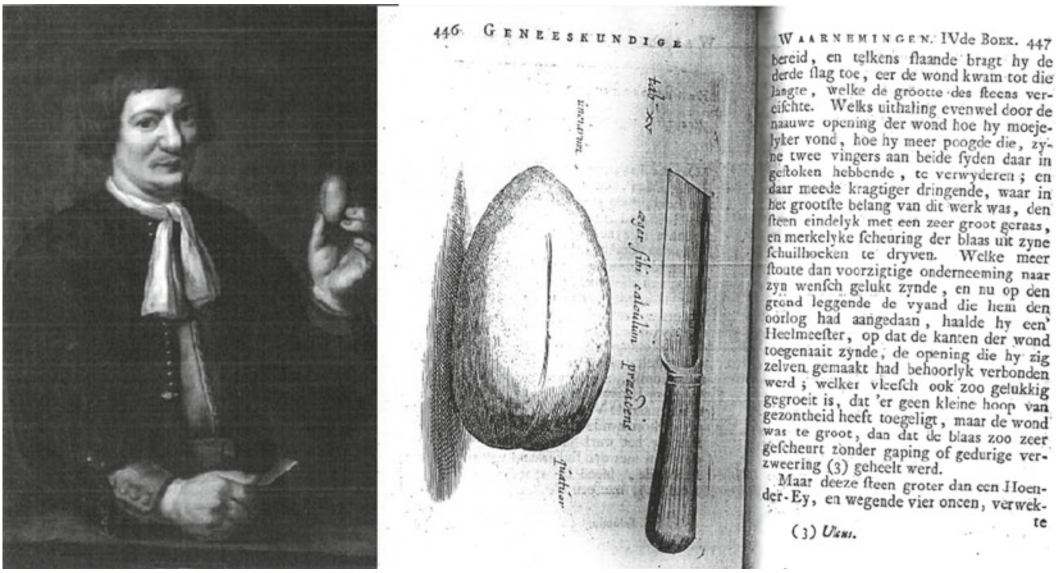

Fig. 7.3 Self-operation on a bladder stone by the smith Joannes Lethaeus (de Doot)

peculiar method of stone extraction: "*When the stone has passed beyond the bladder neck and is lodged in the penis, do not push it back. Gently milk it with your fingers as far as possible, even to deliver it. Help with fomentations of herbs. If you cannot milk the stone all the way out, I suggest that you call on somebody to suck it out. I have used that method several times with success.*"

Paré often quotes the expertise of Franco and, in fact, quotes him quite extensively. He somehow manages to overlook this singular method of stone extraction. Another early commentator, Malgaigne, called this suck method absurd and disgusting. The last known surgical manual to mention this method was G. M. De la Motte in his 1771 *La Chirurgie*. Finally, there is no mention in any of these treatises as to the "specialist" who will provide the negative oral pressure necessary to cause expulsion of the offending urolith [27].

No discussion of medical or surgical treatment during the Renaissance would complete without mention one curious case that clearly points to an unbelievable act of desperation. The story was originally in the works of the famous anatomist/surgeon Dr. Tulp (made immortal by Rembrandt) (Fig. 7.3) [28]. "*Joannes Lethaeus, a Smith, a courageous man, and very astute, who had already been treated twice by a stonecutter, desired so little to be treated a third time by such a man among his daily trials and repeated slayings, that he decided any wild adventure was more attractive to him than subjecting himself to the knife of the stonecutter ever again. Convincing himself that his health could only improve, and having decided that no one but himself would cut into his flesh, he sent his wife to the fish market, which she didn't mind doing. Only letting his brother help him, he instructed him to pull aside his* scrotum *while he grabbed the stone in his left hand and cut bravely in the perineum with a knife he had secretly prepared, and by standing again and again managed to make the wound long enough to allow the stone to pass. To get the stone out was more difficult, and he had to stick two fingers into the wound on either side to remove it with leveraged force, and it finally popped out of hiding with an explosive noise and tearing of the bladder*" [29].

"*Now the more courageous than careful operation was completed, and the enemy that had declared war on him was safely on the ground, he sent for a healer who sewed up the two sides of the wound together, and the opening that he had cut himself, and properly bound it up; the flesh of* *which grew so happily that there was no small hope of health , but the wound was too big, and the bladder too torn, not to have ulcers forming."*

"*But this stone weighing 4 ounces and the size of a hen's egg was a wonder how it came out with the help of one hand, without the proper tools, and then from the patient himself, whose greatest help was courage and impatience embedded in a truly impenetrable faith which caused a brave deed as none other. So was he no less than those whose deeds are related in the old scriptures. Sometimes daring helps when reason doesn't*." [29]. What extraordinary determination and fortitude it must have taken to drive this man to such an act of self-inflicted desperation.

Conclusions

We have spent most of this chapter reviewing the major Renaissance themes of humanism versus scholasticism, human improvability versus preordained penitence, and the ability to learn from nature versus religious dogma. It is impossible to leave the Renaissance period without mentioning an incredibly prolific writer and surgeon who has largely become forgotten in modern times. He developed rather modern notions about medicine, Leonardo Fioravanti. He has now become considered as a charlatan or a quack by some historians, but in one recent work, Leonardo has been referred to as the "*Professor of Secrets*" which discloses the final notion pertinent to the Renaissance of stone disease [30]. Fioravanti traveled extensively and like Paracelsus learned from every possible source the secrets of helping cure sick people. The Renaissance minds were fascinated by secrets: secret potions, secret recipes, secret ingredients, and secret surgical procedures. Leonardo collected these secrets; he used them in his medical and surgical practice and then wrote about them. He personally did not practice lithotomy or stone surgery, but he most certainly prescribed medications, herbs, and concoctions for stone disease in his famous *Theriake* (theriac—universal remedy). He was fascinated by the legendary *Norcini*, specialists who would be called to remove bladder stones. He absolutely hated Realdo Colombo, Michelangelo's physician [30]. These were highly skilled family members who passed down methods of surgical cures from generation to generation. They were natives to the area of Norcia, a village near Perugia in Southern Umbria and now famous for performing reconstructive nose surgeries [31].

One final manuscript draws our attention to the Renaissance treatment of calculus disease, the *Gesuati Manuscript.* It is a compilation by Friar Giovanni Andrea around 1562 in Lucca, Italy, of nearly 400 pages containing about 1,500 remedies [32]. He was from the Order of Saint Jerome which was dedicated to healing the sick. He titled his work *Libro de I Secreti e Ricelle* (Book of Secret Remedies). Friar Andrea describes the secret to break kidney and bladder stones: "*To break the stone in the bladder, take a fox and a hare alive and cut off the heads and carefully collect all their blood*." The blood is carefully mixed with heads, feet, skin, and the liver then dried in an oven to make a powder. This powder is then given to the afflicted with stones twice daily until the stones start to break. This form of "corpse" medication is not at all unique to Renaissance therapeutics; however, the following statement most certainly is significant: "*If you do not believe it, do the experiment. Take a spoonful of this powder and put it in a clean pot with wine or water or broth and also with vinegar, and put in a stone and cover it well and keep it in a warm place for six to eight days. You will find the stone broken into several pieces*" [32]. It is not the treatment that is so remarkable but the interest by the Friar in testing it by observation. Blind faith is no longer considered acceptable. This new method of thinking is not unique to Friar Andrea. This is seen in the works of Paracelsus, van Helmont, Erasmus, Montaigne, Michelangelo, Pictor, Paré, Franco, Fioravanti, and the whole of geniuses from this time of revival. Humans had suddenly become capable of asking question and developing methods to explain and treat problems. This is the Renaissance of the mind that allowed for such broad speculation on the ancient disease of urolithiasis. Perhaps the Paracelsian epitaph applies, "*in herbis, verbis et lapidibus*" (in herbs, words, and stones).

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8 Van Beverwijck: The Bridge from Ancient to Modern

Introduction

The legacy of the Renaissance continued into the seventeenth century and medicine and surgery began to flourish. Lead by a revolution from the ancient university at Padua, the anatomist Andreas Vesalius and Nicolaus Copernicus published two sentinel works in 1543. Vesalius brought the science of anatomy to the forefront of medical investigation by publishing his *De Humani Corporis Fabrica Libri Septem* which directly questioned the authority of the Ancients [1]. This was followed by the physician, Copernicus and his work *De revolutionibus orbium coelestium libri sex* when he demolished the Ptolemaic system of the universe and placed the Earth revolving around the sun [2]. The floodgates were open and the great minds of the later Renaissance would arise in the seventeenth century to start the very foundations of science. By 1609 Galileo had pointed his new telescope (about 30× magnification) at the heavens and observed mountains and craters on the moon; he noticed moons orbiting around Jupiter, that Saturn was irregularly shaped, and that Venus had phases like the moon. In addition, he noted that innumerable were the stars present in the heavens seen unaided by the human eye. The Dutch draper, Leeuwenhoek pointed his equally impressive microscope at droplets of water in 1673 and saw millions of organisms that had never been discovered previously. The Renaissance literati founded the Academy of the Lynx by Federico Cesi in 1606, and the Royal Society was founded in 1660 with the motto "*take no body's word for it*." Inquiring minds wanted to know more; they wanted to change the status quo; they wanted to go beyond the Golden Age of Greece and Rome. Medicine would follow continuing to question the authority of Middle Eastern medicine, the Ancients, and begin the arduous task of understanding disease and health. First, the Greek notion of the four humors would need to be investigated and discarded.

William Harvey and Stone Disease

The notion that stone disease was an imbalance of the humors within the body really limited the physician's ability to investigate the actual causes of kidney stone formation. It was not until a modern foundation in physiology and clinical investigation would disclose the actual causes of kidney stone formation. That such a leap occurred relatively quickly after the foundations of modern experimental physiology were established is no great surprise. In 1628 William Harvey published his landmark text ***De motu cordis et sanguinis in animalibus*** in Frankfurt, Germany [3]. This book is rightly ascribed to a monumental leap in knowledge for it establishes a landmark in both science and medicine. Of course a firestorm of controversy arose regarding much of the precepts, but the floodgates were open and observation and investigation rapidly confirmed the truth of Harvey's observations.

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William Harvey and his historiography is a daunting prospect. Literally, some of the great minds of the history of medicine have lionized him and his contributions to medicine. These include Robert Willis, D'Arcy Power, Sir Kenelm Digby, Sir William Osler, Gweneth Whitteridge, G. Keyes, Kenneth Keele, and Mark Silverman. The old adage *nanos gigantium humeris insidentes* applies in spades. William Harvey was born to a yeoman farmer, Thomas Harvey, on April 1, 1578. He went up to study at Gonville and Caius College at age 16. In 1600, the year that Giordano Bruno was burned at the stake for heresy, Harvey traveled to Padua in the wake of Vesalius and Copernicus to complete his medical education. His professor of anatomy was Girolamo Fabrizio (Hieronymus Fabricius ab Aquapendente) who had just described the valves in veins. Harvey worked tirelessly on his own experiments upon returning to England. He began to lecture to the Royal College of Physicians as well as demonstrate anatomy. In 1628 he finally published his physiologic experimental observations confirming the circulation of blood and the actions of the heart as a pump. This fully overturned the ancient notions of the Greek masters and began the open assault in all areas of medicine to a new method of investigation. Harvey himself suffered from both gout and stones. That he suffered is almost undoubtedly true. His friend and fellow physician, Charles Scarborough, gave him an opium mixture for pain. On one occasion, Harvey is known to have threatened to take an overdose of the powerful pain-killer. Another physician-friend, Dr. Ent quoted Harvey in his last days "*I did not find any solace in my studies, and a balm for my spirit in the memory of observations of former years, I should feel little desire for longer life.*" The suffering had worn Harvey down [4]. In 1652, the basic knowledge and methods promoted by Harvey were applied to our understanding of urolithiasis by Johan van Beverwijck in the Netherlands.

Johan van Beverwijck

Johan van Beverwijck (1594–1647) is one of those physicians who accomplished much during his lifetime, but now is little regarded [5]. As a product of the late Renaissance, he bridges our understanding of knowledge, from the primitive to the modern. Therefore, like so many great minds including some of those considered sentinel, like Rene Descartes, Erasmus of Rotterdam, and Michael Montaigne, he is now a relic of another era. Johan was born and lived for most of his life in Dordrecht on November 17, 1594. His father was Bartholomeus and mother was Maria Boot from a family of successful textile traders [6]. Via his mother's side of the family, he was a nephew to the famed anatomist Andreas Vesalius. He attended Leiden University and graduated with a degree in medicine. He and Cornelis van Someren traveled Caen, Paris, Orleans, Montpellier, and Auvignon following graduation from Leiden. They went on to Italy for visits to Rome and Sienna. They visited Bologna and finally the epicenter of medicine, Padua. Johan stayed and became a student. He like Harvey became enamored with the teachings and work of Fabricius. After graduating he returned to Dordrecht and took up practice and continued his anatomical work with dissections. He was a true Renaissance man, becoming a professor of medicine at the Illustrious School, a librarian as well as bibliophile, a civic leader, as well as a prolific writer [7]. He was a prolific correspondent with many famous people, especially William Harvey [8]. At the end of 1637, Beverwijck wrote a letter to Harvey in which he praised him for his discovery of circulation. Harvey replied to this letter in April 1638 praising in turn Beverwijck's treatise on calculi in the kidney and bladder. Harvey described the work as "*learned and elegant, and truly original*" [7].

Beverwijck's *Treatise*: Chapter One

Beverwijck was a prolific writer. He has a smooth method of writing that was illustrated with examples of patients he has seen or consulted via letters. He is scholarly in his knowledge of the Ancients [9]. He quotes reference after reference from classic medical writings. He speculated about the newest discoveries and the implications to stone disease. This is how he incorporated Harvey's discovery of circulation. He began to move beyond the classic notion that an imbalance of humors and intrinsic heat within the kidneys explained the formation of stones. He is the first major author of a medical textbook to embrace the ideas of Harvey and begin to hypothesize along a new pathway of disease based upon actual physiology. He also expresses some of his own personal observations and experiments regarding stone disease. Beverwijck cannot drop the Galenic principles entirely, just like Harvey who could not disassociate himself with the teachings of Aristotle. They still accepted blindly many precepts that were wrong but yet to be proven ineffective because statistics had not yet been applied to medicine. His method was to compare a range of existing sources from antiquity to the present and add his own observations. He typically would quote experts in medicine currently and offer cases to illustrate his point. He used his own anatomical descriptions of the urinary tract. His book was written in Dutch but was popular enough to have been reprinted several times in the seventeenth century. A close friend Jacob Cats was influential in his writing in Dutch [7]. An English translation was made in 1652, and this version will form the basis of the discussions that follow [9]. This little known book was quite popular in the seventeenth and eighteenth centuries.

Before turning to his book on stone disease, some of his other writings and letters will help focus the discussion. Beverwijck was also a Christian humanist. He believed that humanity experiences illness, pain, and suffering as a result of the Fall—a Christian notion that God's punishment for Original Sin is via pain and suffering. Beverwijck himself suffered from stone disease and may have rarely performed surgery for the disease. He writes in his book on Surgery (*Heelkonste)*: "*All pain consists in the severing of what was put together, and this is its most likely cause. Likewise, the medicine that takes pain away by a countering force does effectively alleviate the pain, but cannot be seen as removing the pain since it only softens it, while the cause remains present*" [7]. This is similar to observations of Harvey and directly comes from Aristotelian notions for unity between mind and body. He admits his source in another medical work entitled "*Treasure of Health.*" "*Our Soul and Body differ a great deal from each other, and are therefore tied together by the intense heat of the body…as Aristotle argues in Book 2, Chapter 4 of his* ***Book of the Soul***" [7]. If this sounds menacingly close to the philosophy of René Descartes, it should be no surprise, because one correspondent of Beverwijck was the French philosopher. Descartes also developed an analytical perception of pain. He suspected that bodily damage and physical pain could be stopped or alleviated by manipulating the reception of the signals by the brain. He also noted that cutting nerves stopped pain, but caused a new type of pain.

The *Treatise on the Stone* is organized in chapters much like a modern textbook of stone disease [9]. Chapter one is an introduction to the anatomy of the urinary tract. There are eleven sections of about 35 pages. Chapter two focuses our attention upon stone disease and there are ten sections. On page 27 in the first chapter, the reader first learns of the discovery of William Harvey and the speculation that this might have significant impact upon kidney stone formation. This follows with almost one hundred pages about stone disease [9].

Section one of the first chapter regards the position of the kidneys. He states that "*the left kidney lies higher than the right one, because the human liver is large and the spleen small.*" In animals (whose kidneys seem to be the only ones examined by Beverwijck) we encounter the straightforward style of the author. We also see his Paduan homage to his predecessors and the rising dissatisfaction with Galen. He continues by attacking a notion of Galen's with the cryptic comment, "*That the kidneys do not suck will be proved presently*" [9]. The idea was that the kidneys actually removed a watery fluid from the body by being apposed to each other on either side of the body. He will use Harvey's notions of blood circulation to attack this notion later in the book. Section two discusses the numbers of the kidneys; they are paired. He discusses ancient notions for the presumptive reason for paired organs. He really adds nothing to this discussion. Section three discusses the shape of the kidneys and is a discussion upon comparative anatomy of kidneys and notes that Aristotle and Plinius made a great deal about their crescent moon shape. Ruminating animals have lobulated kidneys, while bears "*are composed of several small glandular formations the size of cherries*" [9]. Section four is on the nature and substance of the kidneys. In this section, Beverwijck notes contrary to the opinion of Mercatus "*the blood with the chyle of the arteria emulgens or lacteal artery is driven into the kidneys and is purified there of the other whey or watery substance*" [9].

Section five is the longest in the first chapter and is the most interesting to a modern student of stone disease. He begins with speculations of Aristotle that "*kidneys have been given to the animals by Nature in order that they might serve together to stiffen and preserve the blood vessels and that they are misused when serving to dispose of excessive humor*" [9]. He warms to his modernist views by stating, "*As for me, though I cannot deny this function, yet I will not rob the kidneys of their noblest work. For if they have been created merely to cleanse the water, then what is the use of all those veins and arteries distributed through the entire body of the kidneys?*" [9]. He makes some further assertions as to the function of the kidneys by his own personal observations and those of the eminent anatomist Eustachius. He states, "*similarly I feel that the kidneys do not only purge the blood of the whey or excessive water, but also help to boil the blood which they receive in the manner of the liver and spleen. Therefore in bodies of people that have died of diseases, the kidneys generally show alterations. Kidneys which in healthy bodies are red, clear, and solid, according to the illness were found sometimes pale, sometimes brown, sometimes quite soft, fragile and already deteriorated or ulcerated, which has also been stated by the diligent anatomist Eustacius*" [9]. He now brings on an autopsy case of a patient who died with an impacted ureteral calculus and describes pyohydronephrosis, "*The left kidney was larger than usual, quite flabby and soft, entirely filled with pus. On the bottom of the bladder, which was quite fleshy, there was a stone of the size of a walnut enveloped in white slime, which stuck to it when it was removed*" [9]. He is building his observations to a final assault on the blood supply to the kidneys. He at this point reviews all of the ancient notions, invoking Hippocrates, Diocles, Praxagoras, Galenus, Rufus of Ephesus, and Andreas van Wesel to come to his own opinion: "*Now the other blood, separated from the excessive water and remaining after feeding the kidneys, is driven from the arteries into the veins and I think this goes again through the renal vein into the vena cava, impelled by the suction of the heart. I base this supposition on a doctrine which is indeed new, but which in its adequacy and consistency is not surpassed by any of the ancient doctrines, viz. a doctrine of Dr. William Harveus, physician to the present King Charles of England*" [9]. He then goes on to reiterate his understanding of Harvey's work. He uses an epic simile that John Hunter would later reiterate like the running of sap in a tree.

He can now move on to section six where he describes the so-called lacteal vessels (the renal vessels of the Ancients). But he goes into fine detail about renal anatomy. He does a fine dissection of the vessels to try to discover their relation to the collecting system, but he lacks a microscope: "*The vessels both divide and branch immediately, until at last they are as fine as hairs, some of which divide and extend through the entire kidney, others end in the teat-like elevations through which, as through spongy glands the watery fluid is filtered into the tubules that below them extend from the ureter like basins*" [9]. Is he describing a subsystem of vessels of the kidney which would have to await anatomists with microscopes to confirm? Sections seven through ten are further discussion on the anatomy and function of the ureters, bladder, and lower urinary tracts. He notes that the ureters are retroperitoneal structures. He talks about normal versus abnormal bladder anatomy and illustrates a case with a Hutch diverticulum (Fig. 8.1 of his book, Fig. 8.2) [9]. The prostate is clearly present with the seminal vesicles and the ampulla of the vas deferens. He ends the momentous first chapter with a short section eleven that covers normal and abnormal voiding.

Fig. 8.1 Johan van Beverwijck from his textbook *Treatise on the Stone Showing the Origin, Symptoms, Occurrence, Prevention and Treatment of Stone and Gravel*

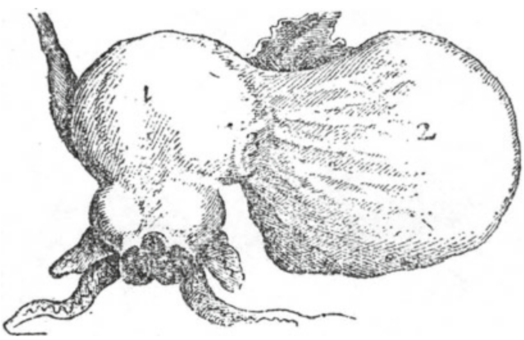

Fig. 8.2 Illustration of the abnormal bladder case from *Treatise on the Stone.* Beverwijck states the case came from D. Causaubon of England

Beverwijck's *Treatise*: Chapter Two

Following the epic first chapter, one would hope that the second which is predominately clinical would also have exceptional insights into this ancient malady. Alas this is not going to be the case. Here he presents ten sections as follows:

1. Stone in various places of our body, but most often in the kidneys and bladder
2. Description of stone
3. Fundamental and immediate causes mentioned by the Ancients, investigated and disproved
4. True causes stated
5. External causes
6. Different manners and places in which it grows in the kidneys and in the bladder
7. Symptoms
8. Prognosis
9. Means for prevention and manner of living
10. Cure [9]

He keeps a running account of ancient writers and their observations and continues to intersperse his own observations and cases from other contemporary physicians. He is trying to break with the notion of blindly following the axioms of ancient physicians; he states, "*I have attempted and experienced, and to compare this with the observations of the ancient and modern physicians, subjecting them to the test of Reason and Experience. For I do not wish to be one of those who, like sheep, merely follow their leader, and who without inquiry simply concur with all that has been left by our predecessors*" [9]. He could be simply stating the common beliefs from his alma mater, Padua. He quotes aptly Lucretius:

> "You'll find then that the base of Truth
> Is founded in our knowledge through the Senses.
> And if the Senses are not quite reliable,
> Then Reason, too, will be to error liable." [9]

He continues by stating, "*It is not necessary here to dwell on the question whether Stone is the disease itself, or the cause, or an accidental circumstance, of little importance to the illness itself. Therefore, beginning our description we say that the Stone is a hard body growing out of an earthy substance owing to inefficiency of the kidneys or bladder and, having hardened into a stony shape, causes very painful tension and obstruction*" [9]. Beverwijck continues by reviewing all of the classic theories of stone formation. Aristotle's thoughts that "*all things harden either by heat which dries the dampness* *or by cold, which squeezes it out*" [9]. He comes to Cardanus' recent assumptions "*that in animals, stones grow by these Aristotelian methods by cold in snails, crabs, etc., by heat in the gall-bladder, kidneys, etc.*" [9]. He goes on to his own autopsy findings and states "*I will try to prove that this slime is no material of which the stone is baked, but merely the remnant of the food which a fleshy bladder sheds*" [9]. Beverwijck believes that there is no heat significant enough to bake or cause a stone to form in the classic Aristotelian sense; he knows that slime or mucus occurs in inflamed bladders and believes that it must be formed by the kidney or bladder. He believes that these slimy emanations are the cause of stone formation, and it fits with the new physiology that the arteries bring nourishment to the kidneys and bladder and that a biologic process is occurring to make the slime, which in turn produces the stone. Beverwijck in this sense disavows chemistry such as expostulated by Paracelsus and van Helmont for a biologic process that follows Harvey's physiology of circulation. This is shown in his next statement, "*The stone, especially if it gains in size, gradually begins to hurt the bladder, which causes pain and weakens that organ. If then the blood does not flow to the bladder, this means that there are other parts, the condition of which is still worse (it is different if the stone lies still). But if the blood does come into the bladder, it is changed there and retained like food, whereby the bladder gradually becomes thicker and more fleshy day after day*" [9]. He is clearly trying to meld his autopsy findings with the physiology of blood circulation and the development of stone disease. He concludes his speculations with an outstanding revelation and includes William Harvey's own opinion on stone formation. This is the only known work that describes a stone formation hypothesis by Harvey: "…*he wrote to me that in his opinion the slime is the matter constituting the stone, because if this slime is merely exposed to the air, it turns to grit, yea to stone in a single night or sooner still, which he states to have observed himself; he even states that he knows a young woman, who used to make little balls of such slime settling in her own water, which ball drying on a plate, hardened to stones*" [9]. He moves onto section five where he hypothesizes that the problem of stone formation is in the urine itself. He does this rather artfully by quoting an absolutely delightful poem from Ovid.

> "*Through the country of the Cicons*
> *Flows a stream that is most strange:*
> *He who drinks it, pays most dearly,*
> *As it will not spare the life*
> *Of a thirsty creature drinking,*
> *Where no thirst is ever quenched.*
> *For, alas! What fearful ailing*
> *Waits him: bowels turned to stone!*
> *All that's floating in this river*
> *Or but moistened with its water*
> *Is at once seen stark and stiffening,*
> *Till it is as hard as marble.*" [9]

We will have to wait until Samuel Taylor Coleridge in the Rhyme of the Ancient Mariner for someone who could write a line that could metaphorically compete with this: "*Water, water, every where, Nor any drop to drink*" [10]. He is desperately trying to get to our modern notion of supersaturation, or an overabundance of the stone forming building blocks. The closest he can get is to use observations then regarding the formation of cave deposits, stalactites, and stalagmites. He quotes another great anatomist from Padua, Fallopius who says "*that a stony liquid being merely stirred in water and not wholly mixed with it, does not change those objects, but only covers their outside with a scale of stone, and the same occurs, when pieces of stone are mixed with water*" [9]. He tries to keep an open mind and states that a physician from Basle Dr. Platerus believes that stones form in the kidneys due to the narrowness and dryness of these organs. He points to the notion of Fernelius "*that all stones of the bladder originate in the kidneys and merely increase and grow in the bladder*" [9]. He discusses as proof Fernelius' notion of the kernel or nucleus of the stones as proof of having arisen in the kidneys. This results in the longest section of the entire text regarding the growth of stones in the bladder. He mentions that prolonged bed rest actually increases the risk of forming a stone; that opium can increase the risk of stone formation; that sharp foods such as radish, pepper-wort, and lemon juice can stimulate the passage of stones; and finally that some types of milk and butter increase the risk of stone formation.

Beverwijck certainly tries to use his senses and observations as well as a wide array of professional associates to influence his thinking and writing. He does go on to discuss surgery and medical therapies and other common considerations of the stone patient. He quotes Plinius [Pliny the Elder] towards the end of his treatise, "*Among all greatest pains, which a man can suffer in his body, the trickling piss caused by stone has of old been deemed the worst*" [9]. He aptly quotes from his fellow Lowlander Desiderius Erasmus as well, "*But I believe that a man whose limbs are cut off one by one, suffers less pain than is suffered by him in whom a stone penetrates through the narrow ureters into the bladder, although the ancient physicians count among the pains that are hardly sufferable, stone of the bladder in the first place. This latter perhaps is therefore worse because it is incurable, unless one desires a remedy more cruel than death and sometimes means death itself. Truly stone in the kidneys comes near this, if it seizes a man badly. It seizes me so often and so terribly that if anybody hates ERASMUS, he should now stop to be his enemy any longer. Further the Stone brings such misery with it, that it sometimes snatches away a body, be it ever so stalwart and strong, within three days. And if it retreats, it does so merely to return the fiercer. What is this but tasting of death again and again? And who would wish to live to die again?*" [9]. He concludes his textbook with an enlightening discussion of stone surgery which he apparently observed but did not perform.

Thomas Sydenham and Herman Boerhaave

Following in the wake of Harvey was Thomas Sydenham (1626–1689). Sydenham is often referred to as the English Hippocrates. He was born at Wynford Eagle in Dorset in 1624 as the fifth son. Sydenham studied at Magdalen Hall of Oxford and volunteered twice in the Civil War on the Parliamentary side, and he was twice wounded. Sydenham studied medicine after being influenced by Dr. Thomas Coxe, a family friend [11]. He married Mary Gee and left Oxford to practice medicine at Westminster. After 3 years of unlicensed practice, he finally passed his examinations and was licensed by the College of Physicians, and he moved his practice to Pall Mall where he spent the rest of his life (except for outbreaks of the plague). He essentially tossed all of the old teachings of classic medicine and began to keep track of his own observations, treatments, and recorded outcomes [12]. Sydenham developed a very practical outlook to medicine; he learned from his patients by performing careful histories and physicals. He wrote details of each patient and disease. He recorded what things worked and what things didn't. He was honest with himself and with his patients. He was presciently interested in both gout and stone disease, as he too would suffer from both maladies: "*Gout produces calculus in the kidney…the patient has frequently to entertain the painful speculation as to whether gout or stone be the worst disease. Sometimes the stone, on passing, kills the patient, without waiting for the gout*" [13]. Sydenham began inconspicuously from Oxford and fought with the forces of established medicine. He befriended many influential people over his years in practice including John Locke who was 8 years younger but idolized his mentor [11]. Hans Sloane who was later president of the College of Physicians and the Royal Society as well as the founder of the British Museum also apprenticed and learned clinical medicine with Sydenham. Robert Boyle, Christopher Wren, and Robert Hooke were all his friends [12]. Herman Boerhaave likewise read and reread all of the works of Sydenham and emulated much of his clinical practices.

In 1683 Sydenham wrote his best-known book *Tractatus de Podagra et Hydrope (Treatise on Gout and Oedema).* In this he linked both gout and stone disease. He, like Montaigne prior to him, noted, "*it might be some consolation to those sufferers from the disease, who like myself and others are only moderately endowed with fortune and intellectual gifts, that great kings, princes, generals, philosophers and many more* *of like eminence, have suffered from the same complaint*" [13]. He continues with the observation that eating and drinking in excess and lack of exercise brought on an attack in those susceptible to the disease. The ideal exercise was riding on horseback. The only effective pain-killer that really worked was laudanum (opium). Sydenham remained puritanical till the very end: "*He suffers until at last he is worn out by the joint attack of age and disease, and the miserable wretch is so happy to die*" [13]. This is hauntingly prophetic to the death of William Harvey that started this chapter though it also could be applied to Erasmus, Galileo, or Isaac Newton. According to his earliest biographer Picard, Thomas Sydenham died in 1689 exhausted by vomiting, diarrhea, and hematuria suffering from calculi.

Herman Boerhaave was substantially influenced by the work of Thomas Sydenham and bridged the last half of the seventeenth century to the enlightened eighteenth century. He was born in 1668 and studied at Leiden taking his degree in philosophy [14]. He began his medical studies in 1691, the year after his philosophy degree was awarded, and he completed his medical degree in 1693. He most likely was self-taught, reading widely on his own though he did attend anatomical dissections [15]. He read the works of Sydenham several times and believed him to be a Baconian physician and follower of the true method of Hippocrates. He did not agree on all the precepts of Sydenham, for Boerhaave valued the legacy of the Ancients as well as the findings of the newer sciences [16]. He particularly valued the findings in anatomy which so disinterested Sydenham. He attracted the attention of the gifted professors Senguerd and DeVolder and was much influenced by the writings of Descartes. He also read Newton and became profoundly influenced by his methods. He was early accused of being a Spinozist, and though he certainly read Baruch Spinoza's works, he was a conservative Calvinist all of his life, but he agreed with the controversial philosopher's ideas of freedom of thought. He would encourage all of his future pupils to think for themselves and not trust in the dogma of published medical opinion. He started teaching medicine in 1701, Boerhaave became the leading light in developing Leiden University as the epicenter of medical learning [17]. Albrecht von Haller (1708–1777) referred to Boerhaave as *communis Europae praeceptor (the teacher of the whole of Europe).* Boerhaave took Sydenham's method of practical bedside medicine and brought it to a teaching university and hospital. Now practical observation and trials were possible and the revolution in medical education had begun; his pupils would populate medical centers of education from Edinburgh to Paris. His magnum opus was *Institutiones Medicae* published in 1708, and he dedicated an entire chapter to urolithiasis. He too would go on to suffer from bladder stones, colic, and gross hematuria. Boerhaave's recommendations for patients with stone disease included an increase in fluids, a hot bath to induce vasodilation, and exercise. Boerhaave thought that stone surgery should be a last resort and that surgery had come far, but had far to go. He said "*I think lithotomy is an act of pure faith*" [17].

Conclusions

The seventeenth century was a time of substantive medical contributions leading to the Enlightenment of the eighteenth century. Beverwijck represents the central focus of the discussions that bridged the gap from the ancient thoughts regarding stone disease, but significant accomplishments also followed from the surgical side. Towards the end of the Renaissance, another sufferer of the stone would keep detailed accounts of his suffering and would later become a member of the Royal Society, the diarist Samuel Pepys. On March 26, 1658, having suffered from stone since infancy, he chose the route of the surgeon: "*I remember not my life without the pain of stone in the kidneys (even to the making of bloody water upon any extraordinary motion) until I was about twenty years of age.*" His brother, mother, and an aunt all suffered from this affliction. As a student at Trinity Hall, Cambridge, he had a violent attack of colic. He turned to Thomas Hollier who was the lithotomist and surgeon at St.

Thomas's Hospital, and the surgery was scheduled at the home of his cousin Jane Turner. He documents a consultation with Hollier's old master who had successfully treated Oliver Cromwell, Dr. James Moleyns who prescribed a soothing draught of licorice, marshmallow, cinnamon milk, rose water, and the white of eggs. The operation was a success, and the stone weighed 2 oz. about the size of a tennis ball. In 1664 Pepys wrote of "*how it hath pleased the Lord in six years time to raise me from a condition of constant and dangerous and most painful sickness and low condition and poverty to a state of constant health almost, great honor and plenty, for which the Lord God of Heaven make me truly thankful.*" He gave a dinner every March 26th which he called "*my solemn feast for the cutting of the stone.*" He had a box constructed to keep the stone in, "*the box cost a great deale of money, but it is well done and pleases me*" [18].

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9 Enlightened Minds and Stone Disease

Introduction

The eighteenth century is remarkable for the development of our modern notions such as science and technology in an increasingly sophisticated and mechanical world; it is the age of adoption of the humanistic precepts of the seventeenth century coupled with awareness that via experiment, knowledge could transcend even classic learning. There were great expectations for man's potential but also great recklessness in man's ability to wage war with the French King Louis XVI getting beheaded on January 21, 1793, and the rise of Napoleon Bonaparte just 5 years later. As with all of our previous chapters, there is no absolutely defining moment that identifies the Enlightenment, but the zeitgeist (spirit, Herder 1769) is best summarized by Voltaire, the literary master. The Enlightenment also saw the institutionalization of knowledge by the creation of encyclopedias.

The French *Encyclopédie*, *ou Dictionnaire raisonnè des sciences*, *des arts*, *et des métiers* of Denis Diderot (1713–1783) and Jean-Baptiste le Rond d'Alembert (1717–1783) epitomizes this period of human accomplishment. The *Encyclopédie* was first released in Paris in 1751 and sold more than 4,000 copies [1]. It was written for the average intelligent person and their families. Medicine figured prominently in the writing which was classified in the physical sciences. There were 139 handpicked contributors to the *Encyclopédie*, and the medical giants mostly from the continent came forth. The sections on the kidney and stone disease were at the forefront of the times [1]. "*The kidneys are 2 paired extraperitoneal organs*. *They are located between the lumbar ribs and muscles*, *on the right and left side of the spine*, *and are embedded in a fatty environment…The kidneys are the most dense visceral organs*, *move with respiration*, *and the lower pole of the right is below that of the left side*. *In the kidney*, *one distinguishes a cortical part*, *which is yellow*, *soft*, *and highly vascularized*, *and a medullary part*, *which is more dense*, *whiter*, *and more consistent*, *made of lobules*, *which in adult humans are joined together*. *Here*, *we recognize pyramidal structures of different size*, *in which are columns consisting mainly of tubular conduits*" [2]. This is a modern method of description which could be read in any current textbook. They try to keep current by proceeding to physiology and speculation: "*For Malpighi*, *the kidney was a glandular organ made by small arteries forcing their fluids into a spherical cavity continuous with a small urinary conduit*. *The most colored part of the blood is separated in these glands*" [2]. This represented the microscopic findings of Malpighi. It goes far beyond the hypotheses of van Beverwijck and incorporates all of the newest scientific findings. He continues "*It cannot be doubted that urine is brought to the kidney by arteries*, *is poured in the urinary conduits and received into the ureter*." He continues "*An identical road is covered by lithic matter or the calculous clot preceding stone formation*" [2].

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The Enlightenment would also see the rise of philosophers: Francis Bacon, Burke, Condorcet, Hobbes, Home, Hume, Kant, Locke, Rousseau, Adam Smith, Baruch Spinoza, and Wolff. The writers included the following: Boswell, Gibbon, von Goethe, de Gouges, Hobbes, Voltaire, and Mary Wollstonecraft. The political thought leaders included Boehmer, Burke, Condorcet, Benjamin Franklin, Alexander Hamilton, Jefferson, Locke, Madison, Montesquieu, and Paine. The natural philosophers deserve special attention and include d'Alembert, Berkeley, Buffon, Franklin, Hooke, Lavoisier, Leibniz, von Linné (Linnaeus), Isaac Newton, and Volta. The literal outpouring of knowledge was certainly not limited to these giants; this was also the time of Mozart and James Cook and the Reverend William Paley who developed his influential rationalization of religion. But it also ushered in the first outspoken atheist in Baron d'Holbach and the most ostracized philosophy of Spinoza (which quite possibly best summarizes our current brain physiology of consciousness) who was vilified by all major religious faiths.

Stone Disease and the New Medicine

From the beginnings of Leyden (Leiden) as a famed medical school came a little known Scottish physician Pitcairne. He was to leave Leiden opening the way to Boerhaave and returned to Edinburgh and influenced the minds of Reverend Stephen Hales and Dr. Robert Whytt. Edinburgh would gradually rise to become the leading light of medical knowledge as the Scottish Enlightenment would also eclipse the Western world. Stone disease was on the rise, and certain communities noted especially high prevalence rates, such as Norwich in England. William Cheselden (1688–1752) became the surgeon at St. Thomas's Hospital in London and achieved fame as a lithotomist. But first a digression is necessary to Joseph Priestley (1733–1804), an enlightened mind if ever there was one. His intelligence was applied to many areas but we are interested in his notion of Phlogiston and fixed air. He published his work "*Consideration on the Doctrine of Phlogiston and The Decomposition of Water*" in 1796 [3]. He literally was taking some of the notions of van Helmont and adding to them. Antoine Lavoisier (1743–1794) would have major controversial disagreements with the experimental observations of Priestley, and even some of Priestley's devoted friends such as Dr. Erasmus Darwin fellow member of the Lunar Society would side with Lavoisier [4]. Yet, carbon dioxide as we now know it would become the basis for modern chemistry, especially organic chemistry.

Others would pick up the thread of fixed gas and begin to investigate common substances, especially calculi which were beginning to get collected by surgeons. The Reverend Stephen Hales (1677–1761) was one of those investigators (Fig. 9.1d). Hales was born at Bekesbourne near Canterbury Kent on September 17, 1677. Hales matriculated at Cambridge in the spring of 1696 and was elected as fellow at St. Benet College in 1703. He worked on plant and animal physiology with his lifelong friend Stukeley and was interested in medicine by interactions with Pitcairne at Edinburgh. He was enamored with chemistry and repeated the experiments of Boyle [5]. He read and digested Newtonian physics. He left Cambridge and became a minister of the parish of Teddington in the County of Middlesex in 1709. His mind was curious and probing, and being a minister, he had ample time left for experimentation. Hales began a series of experiments in physiology and chemistry, and he began to send his writings to the Royal Society: "*The Rev: Mr Hales informed ye President that he had lately made a new experiment upon the effect of ye Sun's warmth in raising sap n trees. Mr Hales was desired to prosecute these experiments and had thanks for communicating the first essay*" [5]. This was logged into the Royal Society Journal Book in 1718. These studies were eventually published in a book *Vegetable Staticks*. He followed with a series of experiments that made him famous on blood pressure determination, but he became engrossed in stone disease [6]. He may have been following up on some of the investigations of Boyle, but he was well aware

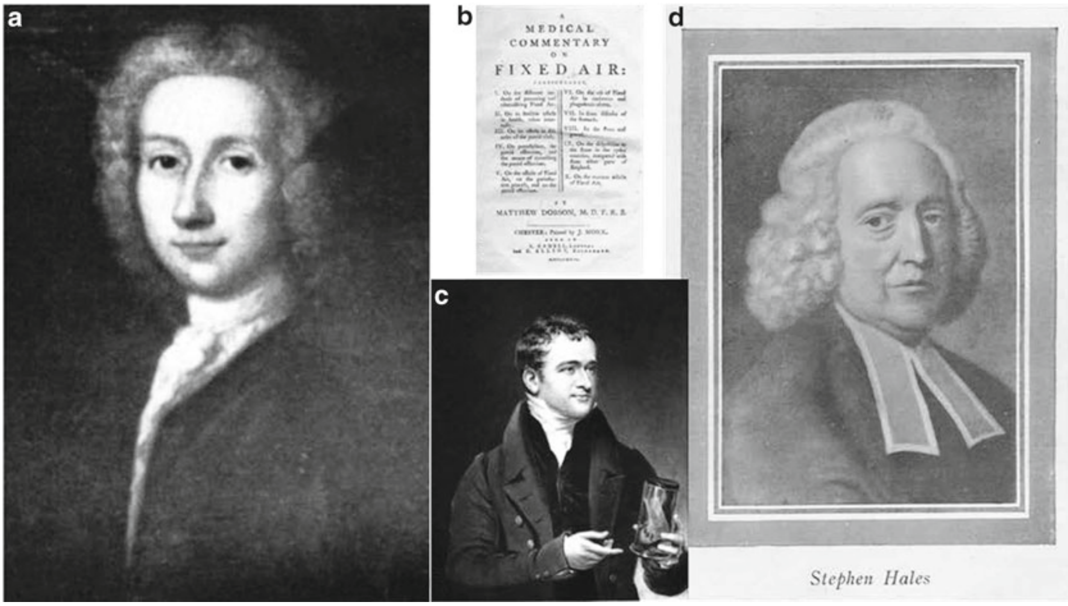

Fig. 9.1 (**a**) Robert Whytt. (**b**) The book by Matthew Dobson "A Medical Commentary on Fixed Air." His only known portrait was accidentally destroyed by house staff junior surgeons in Liverpool. (**c**) Karl Wilhelm Scheele. (**d**) The Reverend Stephen Hales

that "distemper of the stone" was a common condition throughout England [5]. He resolved to do some chemistry on the stone in search of a method of dissolving these concretions. He even invented a double-lumen catheter to deliver his solutions in canine (dog) experiments.

Hales had an amazing quality for grasping complex problems and thinking them through and, even with little information or experience, would intuit solutions that eventually would become accepted. Not only did he develop a double-lumen catheter; he also devised an ingenious forceps device that could extract urethral stones that would eventually get rediscovered by the likes of John Hunter: "*I cut off the lower end of a straight Catheter for a Stillet or Forceps to pass thro*'; *the lower end of the Forceps was divided into two Springs like Tweezers who Ends were turned a little inwards*" [6]. His writings and investigations on calculus disease were eventually published with his sentinel work on blood pressure. In 1739 he was awarded the Royal Society's Copley Medal for this work. In order to develop a solvent for stones, he needed to understand the nature of the stones themselves. He subjected bladder stones to a blowpipe and tried to understand their chemical composition [7]. He used preparations of nitric acid and sulfuric acid and measured their responses. At one point he wrote, "*I suspect that the principal Cause of the first beginning of the Growth of Gravel in the Kidnies*, *is owing to the horizontal Posture we are in when we lay in Bed*: *In which Posture one of the Kidnies being lower than the Bladder when we lay on one Side*, *and both the Kidnies when we lay on our Back*; *the Pelvis or Cavity of the Kidnies becomes thereby the Sink for the tartarine Parts of the Urine to settle in*" (228) [7]. He uses his understanding of physics to speculate further: "*Progress of the Urine being in some degree retarded*, *it has more time to deposite its Tartar in those small Ducts in the Papillae*, *where it is thought the first minute Beginnings of Gravel are usually formed*; *it being in Dissections found there*" [7] (Randall's plaques and the modern hypothesis of Dr. Marshall Stoller). Later in his life, he became involved in the nefarious incident by the government in purchasing Joanna

Stephens' medicine. He wrote "*An Account of Some Experiments and Observations on Mrs Stephens' Medicines for the Stone*." in 1740 [8].

Robert Whytt is another forgotten player on the stage of medicine (Fig. 9.1a). On October 19, 1903, a disciple of William Osler read a tribute to the history of this physician at the Johns Hopkins Hospital Historical Club [9]. Whytt trained at the new medical school in Edinburgh between 1730 and 1734. He went to London and worked with Cheselden. He went to Paris and attended the clinics at La Charite and the Hôtel Dieu. He then went to Leiden to listen to the ancient professor Boerhaave and his heir Albinus. He took his medical degree from Rheims which was commonly done by Brits [9]. In 1747 he was chosen as the chair of the theory of medicine at his alma mater which he then held for the rest of his life. In 1743 he published his "Edinburgh Medical Essays." In this work, he presented a paper "On the Virtues of Lime-Water in the Cure of Stone." This paper and work was triggered also by the controversial medical cure of Mrs. Stephens that had attracted Hales. Whytt thought that limewater might be a better delivery agent and began to prescribe it to his stone patients by 1741. He seems to have had a good deal of success and usually mixed this with soap. Whytt's treatment was to give an ounce of Alicant soap and about three pints of limewater daily. The alkalinity of this solution probably had some effect on uric acid stones that predominated in his patient population. He went on to perform numerous experiments ex vivo with his limewater and did honestly note that it did not perform as a universal solvent, similar to the findings of Hales. He investigated numerous other water sources and discusses some controversial aspects of stone dissolution at odds with Dr. Alston. He expanded his stone studies and published them in 1750. His work probably triggered the interest in Black to investigate calcareous earths and fixed air. Whytt became suddenly ill and died in 1766. His collected works were published by his son and Sir John Pringle in 1768 [10]. Seller summarized the sad loss of this accomplished individual by stating "*In short, Whytt, though of an ardent temper, really was a man of well balanced feelings, earnest after truth, not unsolicitious of fame, whole all the sentiments he expresses indicate a benevolent turn of mind, full of love to mankind, and a determination, at any cost to himself, to fulfill the duties of his station*" [9].

Protochemistry

Karl Wilhelm Scheele (1742–1786) has been referred to as "hard-luck Scheele" by Isaac Asimov because even though he made many discoveries before others such as Priestley, Davy, and Lavoisier, he seldom got credit because he did not publish timely or in places that were widely read (Fig. 9.1c) [11]. Scheele was born in Stralsund, Sweden, on December 9, 1742 [12]. He came from a modest background and apprenticed as a pharmacist in Gothenburg for 8 years. He then worked as a pharmacist in Stockholm, Uppsala, and Köping during his life. He also became profoundly interested in chemistry and performed many experiments. In 1776 Scheele turned his inquiring mind to urinary tract calculi [13]. He revealed that the main component of a bladder stone was a substance that was barely soluble in cold water but was an acid that turned litmus paper red. This substance dissolved in alkali and precipitated in acids. He dissolved this substance in hot nitric acid which he was able to isolate following evaporation which was a pinkish crimson color. He heated this in a flame, and it gave an odor like prussic acid, ammonia, or burnt horn [13]. He described these revolutionary findings at the Academy of Sciences in Stockholm. He named his substance lithic acid, and he stated that it was the major component of all stones.

Andreas S. Marggraf (1709–1782) is similar to Scheele except the fact that his writings were presented in Berlin and written in French. He also was the son of a pharmacist and became an adept chemist [14]. Like Scheele he devoted himself to new chemical methods. He attended medical school for 1 year in 1725 but became increasingly focused on chemistry. He simplified and explained the phenomenon of phosphorus in the urine and developed the chemistry of

Fig. 9.2 Rare colored rendering of Andreas Sigismund Marggraf (1709–1782)

phosphoric acid. Marggraf also developed a colorimetric analysis of various forms of phosphates. He is the first person to chemically note that there are different types of urinary stones based on composition. Berzelius confirmed these findings and those of Scheele. Marggraf's collected works were eventually published as *Chymische Schriffen* in 1766 [15]. Marggraf's contributions are typically overshadowed by the work of Scheele and the founders of chemistry, but his contributions were crucial; there is one known likeness image of him, a simple watercolor (Fig. 9.2).

Matthew Dobson, M.D., F.R.S.

Matthew Dobson (1732–1784) could almost be seen as the opposite of Reverend Stephen Hales. Dobson was born in Yorkshire, was the son of a Nonconformist minister, and was expected to follow in his father's footsteps. He, however, discovered medicine as a career within Edinburgh where he graduated in 1756. He developed a wide range of interests and was soon experimenting on many areas of physiology and medicine. He began his clinical practice in Liverpool in 1762 and became one of the founding physicians at the Liverpool Infirmary in 1770. He became interested in urinary stone disease and corresponded widely with the Royal Society and published in the Philosophical Transactions. Matthew Dobson first reported 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 30 times higher than those admitted to Cambridge Hospital. In Worcester, Hereford, and Exeter hospitals, there was 1 stone patient among 394 admissions. In northeast England including Newcastle, York, Leeds, and Manchester, the ratio was 1/420. In Liverpool, Chester, Shrewsbury, and North Wales, it was 1/3,223. He concluded that stone disease was more common in the "Cyder" districts and that hard water prevents rather than promotes the formation of stone disease. Quite the unexpected finding! He also began to investigate the ability of alkaline soap and limewater to aid in the treatment of stone disease, but unlike Whytt, he was significantly less impressed and noted it did not help in some cases of stone disease. He wrote his treatise "A Medical Commentary on Fixed Air" in 1779 (Fig. 9.1b).

In this work, it is Chaps. 8 and 9 that attract our interest. Most of the work is a series of experiments and clinical observations. Chapter 8 is called "In the stone and gravel." Chapter 9 is called "On the disposition of the stone in the cyder counties, compared with some other parts of England." In the introduction of this book, he gives credit to his sources prior to his experiments: "*…we find also*, *from the experiments of Dr. Hales*, *Sir John Pringle*, *Dr. McBride*, *and others*, *that Fixed Air enters very universally into the composition of animal substances*." He reviews the findings of virtually all pertinent information to this time including the works of Priestley, Lavoisier, van Helmont, Hoffman, Cavendish, Lane, Bewley, and Venel. He begins Chap. 8 with the comment "*An accurate and ingenious* *philosopher, the Hon. Henry Cavendish, has pointed out, by a connected train of experiments, that calcareous earths are made soluble in water, by being united with more than their natural proportion of Fixed Air*" (128–29). He moves onto some experiments but returns to the thesis "*This doctrine of the solution of calcareous earths, naturally suggested the idea of the solubility of the human calculus while yet in the bladder, by the regular and continued use of Fixed Air.*" He is trying to define the notion of supersaturation of solutes with an interaction of carbon dioxide. He does not know about the conversion by the kidney into bicarbonate ions and the buffering effects of citrate, but he is getting remarkably close to modern urine biochemistry. He quotes a study from the eminent physician and ethicist who experimented upon a test subject, Dr. Percival: "*A young gentleman…has, at my desire, taken large quantities of mephitic water daily, during the space of a fortnight. And whilst he continued this course, his urine was strongly impregnated with Fixed Air, as appear'd from the precipitation which it produced in lime-water; from the bubble which it copiously emitted when placed under the receiver of an air-pump; and from the solution of several urinary stones, which were immersed in it*" (132–33).

Sampson Perry, Surgeon

Towards the end of the eighteenth century, a surgeon wrote a treatise entitled "*A Disquisition of the Stone and Gravel; with Strictures on the Gout, When combined with those Disorders.*" This was Sampson Perry who published his textbook in 1772 from London and dedicated it to the Royal College of Physicians. He was born in 1747 in Aston and practiced surgery in London through the 1760s. He joined the East Middlesex Militia in 1765 and became a captain during the American War of Independence. He was twice honored by King George III. He became a newspaper owner/editor for the *Argus* that evolved increasingly radical political views and supported the French Revolution [16]. He was contemporaneous with other liberal intellectuals including James Parkinson and Thomas Paine.

His textbook *A Disquisition of the Stone* sold well, and he came out with a seventh edition by 1785 [17]. He begins his dedication by stating candidly "*In respect to that part, which treats of the discovery of a cure for the stone, I flatter myself the world will do me the justice to view it in its proper light, particularly as I have not dealt in conjectures, but in matters of fact*" [17]. He continues in his preface by stating that he is a surgeon and will bring a surgeon's perspective to his discussions. He has two postulates that he puts forth early: first that stones form in the kidney and are conveyed to the bladder and second that once in the bladder, they can grow and enlarge which then causes troubles [17]. He also attacks the widespread attempts of the previous authors of the Enlightenment by showing that it is very difficult to dissolve stones with any solvents in humans. His first seven chapters concentrate on stone disease, and in the final chapter, he discusses gout. Perry discusses some of the unique properties of urine: "*That the urine is an elementary fluid, or rather made up of elements, is evidently demonstrated by the frequent experiments made on it by chymists, from which they extract an insipid lymph, a volatile spirit, an acid saline matter, some oil, and a fixed earth*" (9). He builds to a crescendo and names the causation of stone disease in Chap. 3, Section "Physicians and Suffering." He states that "*human calculi are of very different degrees of density and cohesion; some being so loose and friable as to crumble to pieces between the fingers, while others have been taken from the body, of such a compact and flinty nature, as to strike fire in collision with steel…*" (25). In Sect. 2, he discusses the suppositions of others as to causality, and he specifically addresses the drinking of water, the climate, and the food that are all implicated in stone disease. In Sect. 3, he discusses the microscopic characteristics specific to the kidney and uses the measurements of Lieuenhock [Leeuwenhoek] with tubule diameters of 1/80,000 of an inch to begin to build to his hypothesis that these small tubules represent the site of stone formation [17]. He next describes some ingenious experiments where he places human stones in urine of non-stone formers and stone formers to measure change in mass.

In Chap. 3, Section "Physicians and Suffering," he announces what he believes is the cause of all stone formation he titled "Of the Real Cause of the Stone" [17]. He believes that the elemental particles that produce the stone separate from the blood in the tubules of the kidney, and he names them "*primary particles of stone*" (48). Once the primary particles are separated from the blood in the tubules of the kidney, "*those primary particles so as to become a nucleus of the stone*: *for*, *from the second experiment of the same section we find*, *that when once a nucleus exists in the body*, *it collects by its attractive power*, *the particles abut its surface*, *and thereby accumulates continually*" (48). He believes all the centers of stones are these nuclei and that they all form in the kidney. Bladder stones form from stones that began in the tubules of the kidneys and have passed down the ureters to the bladder. This is also a remarkably modern concept. He is not the chemist that Priestley, Hales, Scheele, or Marggraf is, so he does not know that stones are formed from different chemical components, but he essentially is getting to the modern notions of nucleation, fixed particle retention, and supersaturation. He would live the remainder of his life running from his radical politics. First warrants for his arrest in England forced him to flee to Paris at the height of the "reign of terror." He was imprisoned in Paris for 401 days and was sentenced to the guillotine but escaped with a rather remarkable stroke of luck and daring. On returning to England, he was promptly arrested again and imprisoned for 8 more years which he spent writing a history of the French Revolution [16]. Almost no one credits his writings as a physician in the modern era.

Discussion

The eighteenth century saw the rise of scientific inquiry and the acceptance of the Industrial Revolution by the Western world. Sir Isaac Newton proved beyond a shadow of anyone's doubt that applied mathematics and science was a potent combination and the world shuddered. But Newton was always a reclusive sort and began to suffer with bladder stones, obstruction, and gross hematuria: "*In August*, *1724*, *the presence of a dreaded disease declared itself by his voiding without any pain*, *a stone*, *about the size of a pea*, *which passed in two pieces*" [18]. His health continued to decline, and he resigned his post at the Royal Society secondary to bouts with painful gout by 1725. On March 4, 1727, Newton experienced severe pains and his physician diagnosed a bladder stone: "*The pain rose to such a height that the bed under him*, *and every room shook with his agony*, *the wonder of those that were present*" [19]. The great mind of his time would stand no more on the shoulders of giants.

Bartolomeo Eustachio's (c.1500–1574) illustrations were lost until rediscovered and published in 1714 by Lancisi [20]. They revealed an unparalleled degree of observation by this great anatomist, including the renal tubules that had been rediscovered by Bellini [21]. Marcello Malpighi (1628–1694) extended these observations with microscopic examination of the kidneys and the first description of the glomerulus in his *De Renibus* in 1666 [22]. He hypothesized that "*For the most part the abnormalities appearing in the urine spring from disease of the blood coming to the kidneys*, *and particularly those hereditary diseases whose diathesis is not developed in the structure of the kidney*, *but is in the blood*." Malpighi would hypothesize that stones originally formed in the renal tubules and resulted in progressive renal damage: "*Now it frequently happen that small stones are held in these membranous ducts and are enlarged by the accretion of tartar*, *so that they injure the delicate membrane of the vessels and consequently the flesh of the kidneys is often observed to be destroyed*" [23]. The child prodigy and gifted pupil of Malpighi's heir Valsalva, Giovanni Battista Morgagni (1682–1771) would take the next logical steps [24]. He studied medicine at age 15 and assumed the chair of anatomy at Padua at age 33. In his towering work *The Seats and Causes of Diseases Investigated by Anatomy* in 1761, he detailed observations on autopsy of patients with stone disease. In Book II, letter L, article 15, he states "*But as we see it so often happen*, *that one kidney not secreting*, *or not emitting urine*, *by reason of its being corrupted*, *on account of obstructing calculi*, *is supplied by the other*, *and* *that this is confirmed by the very increase of it*." He articulately describes compensatory hypertrophy of the contralateral kidney. Morgagni specifically alludes to this hypothesis noting a case of infant stone disease: "*And there are urines which deposit these particles sooner*, *and more readily*, [*Brendelius*] *does not at all doubt*, *where he mentions the cases of two infants*; *one but just two days old*, *and the other about eight*; *who not only dischrg'd calculi before death*, *but had calculi found with them when dead*" [25]. He continues "*In summer the calculous matter is much less diluted by the watery matter*, *which then goes off*, *through the skin*, *in a very considerable portion*: *and this seem to me another reason why*, *if it is in our power to choose*, *the excision of the calculus should be put off from autumn to spring*, *rather than from the spring to autumn*" [25]. This is a remarkably modern insight; it presages the seasonal incidence of stone disease and presents the etiologic reason for "stone belts" that has to do with insensible fluid loss and dehydration. He concludes in Book III, letter XLII, article 20, with one of the first descriptions of stone formation upon a foreign body: "*a country girl…died in her fourteenth year. For having introc'd a brass hair-bodkin*, *notwithstanding it was bent in the middle*, *very high into the urethra*,*…she was silent as to the true cause of the pains. For even the bodkin could not be extracted*, *by reason of a calculus that was form'd upon it. But the ureters*, *and the kidnies themselves*, *were in a very bad condition indeed*" [25].

John Bostock (1773–1846) was a physician and trained apothecary who also studied medicine in Edinburgh and Leiden then became a junior physician with Matthew Dobson in Liverpool [26]. He worked with Joseph Priestley and became a transitional figure with many of the early modern founders of stone chemistry in London. He was contemporaneous to Wollaston, Marcet, and Michael Faraday. He published on the chemistry of urine in 1805 and 1813, and he followed these with autopsy findings later in the nineteenth century [27]. He influenced William Prout and was a mentor to Richard Bright, all of whom we'll meet in "Founding Fathers" chapter. The shadows of the future of medicine would come hauntingly quick from the brilliant mind of a physician doomed to shine bright and burn out like a supernova, Marie-Francois Xavier Bichat. He was a young French anatomist who wrote four books with limitless possibility for medical science and died of tuberculosis on July 22, 1802, at the age of just thirty [28]. Bichat stated "*you may take notes for twenty years*, *from morning to night at the bedside of the sick*, *upon the diseases of the viscera*, *and all will be to you only a confusion of symptoms*, *- a train of incoherent phenomena. Open a few bodies*, *the obscurity will disappear*" [29]. We began using Francois-Marie Arouet de Voltaire as the eponymous figure of the Enlightenment. In a little discussed work from this prolific writer (over 2,000 books and pamphlets), he wrote "Extreme." He chose medicine as a metaphor to man's progress: "*The first man who at the right moment bled and purged a sufferer from an apoplectic fit*; *the first man who thought of plunging a knife into the bladder in order to extract a stone*, *and of closing the wound again*; *the first man who knew how to stop gangrene in a part of the body*, *were without a doubt almost divine persons*, *and did not resemble Moliere's doctors*" [30]. The Enlightenment came to a close, and Voltaire said in *Candide*, "*The dread of depriving man of some false liberty*, *robbing virtue of its merit*, *and relieving crime of its horror*, *has at times alarmed tender souls*; *but as soon as they were enlightened they returned to this great truth*, *that all things are enchained and necessary*" [31].

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10 Charlatans, Quacks, and Joanna Stephens

Introduction

> Urina est meretrix, vel mendax (Urine is an Harlot, or a Lier) [1]

Stone disease never seemingly fit into the nice "cubby hole" of classic Greek and Galenic thought of humoral imbalance that many common illnesses did. There was no widely recognized treatment in the armamentarium of the average physician, and the incidence of stone disease was prevalent. The average yeoman farmer and his family could ill afford the costly prices of the medical profession. It is no surprise that roaming quacks had ample access to customers in this setting. Urine was known since antiquity to have certain colors, clearness, and sediment, and the use of an ancient medical instrument, the macula, was widely employed to illustrate these properties by some doctors throughout the Middle Ages [2]. There were whole treatises on the use of urine inspection to aid in the diagnosis and treatment of patients. By the late Renaissance, physicians began to question the dogma of complex regimens involved in the prognostication of disease by urinalysis. Thomas Brian, a young idealistic physician, wrote a treatise questioning the ability of anyone to diagnose and treat simply by examining urine in his series of lectures entitled "*The Pisse-Prophet Or Certaine Pisse Pot Lectures*" in 1637 [1]. The great British physician and anatomist Thomas Willis (1621–1675) wrote a treatise entitled "*Treatise of Urine*" against "piss prophets" and the inappropriate utilization of urinalysis to diagnose disease [3]. Willis is essential for our tale of stone disease for several reasons, though he is well known for his contributions to brain anatomy (the circle of Willis); he also wrote extensively on medical therapeutics and commented on stone disease. In this context, he utilized some of the more bizarre therapeutics though not limited to English Paracelsian or Helmontian iatrochemists including Sir Kenelm Digby and Robert Boyle, the "*skeptical chymist*" [4]. Willis occasionally recommended distilled human urine to help alleviate the suffering from stone disease. He also is the first modern English author to recommend routine tasting of urine for diagnosing diabetes mellitus (he coined the word from earlier sources).

The urine distillation was quite specific and probably derives from the German Paracelsian chemist Johann Schröder (aka Schroeder) who published *Zoologia: or, the History of Animals as they are Useful in Physic and Chirgery* in 1659 [5]. Johann extols the virtues of animal parts as well as human parts in the treatment of diseases. His Chapter XXIII is on the use of *Homo* such as blood, fat, urine, and sweat as well as from the *Carcasse or Dead Man*. His treatment for stone disease consists of the "*urine of a boy twelve years old, who drinks good wine*" which is distilled into a spirit (alcoholic) form and drunk to expel the stone. Schröder admits that the concoction "*stinks grievously*" and sensitive patients might not have the stomach for it and calls it appropriately "Vertus." He offers an alternative form of delivery that is the medicine injected

M.E. Moran, *Urolithiasis: A Comprehensive History*, DOI 10.1007/978-1-4614-8196-6_10,

directly into the bladder via the urethra with a syringe [5]. All in all, Schröder discusses the use of almost all types of mammals, fish, birds, and insects, a true cornucopia of medicines derived from living creatures including humans and their excrements.

Charlatans and Secrets Become Respectable?

In the whole history of arcane medical therapeutics, the Pharmacopoeia has a long list of bizarre remedies ranging from feces to ground mummy. One inclusion, rarely alluded to in modern discussion, is the "tongue stone" or glossopetrae. This ancient medical cure has a long lineage that includes the medieval cure for the worst cases of poisoning as well as renal colic. In the works and writings of a rather unheralded seventeenth-century physician Niels Stensen or Steno (1638–1686), there exist some assertions regarding a rather unorthodox treatment for disease [6]. Stensen was a brilliant scholar and anatomist (Stensen's duct) but discovered and described that glossopetrae were the fossilized remains of sharks and went on to describe the early laws of geology. Stensen was at the court of the Medici in Florence, a member of the Lyceum, when serendipitously a large shark was caught, and he was asked to dissect the head. He noted that the teeth were the same as the medicinal glossopetrae used by physicians in the region. His investigations and writings started a new science, geology [7]. Tongue stones have been utilized for centuries by Maltese physicians and throughout the Roman Catholic world. St. Paul apparently overcame a lethal bite of serpent utilizing tongue stones. Glossopetrae have many uses in folk medicine from preventing injury by many poisons, easing difficult childbirth, and aiding in the passage of calculi [8]. But their real legacy lies in prompting Saint Nicolaus Stenonis (Latinized after his becoming a Catholic priest), canonized in 1938 and beatified in 1988, to investigate the rocks and strata of the Tuscany region to accurately develop the principles of modern geology.

Disease cannot be completely separated from faith and religion, so it should come as no surprise that prayer and disease should have some religious overtones. Stones certainly have been considered for ages as a particular punishment for sin and that repentance and prayers have held a dominant position for centuries. Monarchs have also developed specific qualities over the ages that could have influence over the natural history of disease. Though only lawful monarchs possessed this mystical power, often called the "healing touch," it might well have been used on stone sufferers, though mostly known for treatment of scrofula (infectious lymphedema). Both kings and queens wielded this mystical power in often elaborate ceremonies. Special gold coins called "touch pieces" were often given to the sick as well or in lieu of actually being touched [9]. Henry IV of France is estimated to have "*touched*" upwards to 1,500 ill patients at one time. Queen Anne (d. 1714) is the last English monarch to carry out this practice, but Louis XV touched over 2,000 people during his reign. But Charles II, a believer in Paracelsian medicine, was a confirmed believer in his innate mystical powers of touch. He probably curatively touched over 90,000 people during his 20-year reign [9]. He also had Dr. Clerke dissect a man and woman before his majesty in early 1663. He was so fascinated with anatomy that he reportedly himself dissected an infant baby boy and kept the cadaver in his presence for a week (it might actually have been his illegitimate son born of one of his mistresses, Winifred Wells) [10]. Recounting these rather sordid tales of Charles II helps us consider his fascination with "corpse medicine" and his alleged payment of £6,000 for Goddard's secret recipe of powdered human skull and moss (unsea) [10]. This medicine was from thence referred to as the "King's Dropps" and used widely for many ailments and pains, including stone disease even into the nineteenth century (skull therapy).

Bezoars and amber are other ancient therapeutics that had been widely recommended for kidney and bladder stone patients. These both made it into the *Pharmacopoeia*. Bezoars are the concretions that form within the bodies, typically the gastrointestinal tract of animals. The most notable of the bezoars derives from the porcupine which apparently develops large gallstones that were harvested for their therapeutic efficacy [11]. There are no reported or known outcomes of patients treated with this substance, but it can well be imagined that because of the rarity of this material, it was costly. It is also likely that the physicians and apothecaries that dispensed this unusual substance quite possibly did not disclose the true nature of their cure. Amber is another naturally occurring substance that had a very long lineage in therapeutics for stone disease. Actual usage of this mineral substance derived from fossilized tree sap was widely traded because of its rarity and unusual characteristics such as color and clarity. It could be ground, liquefied, and worn as an amulet to draw out the badness. Amber is known to have been collected since Neolithic times but when it was first utilized to treat stone formers is lost in time. Amber gets its name from the Greek sun god Helios with the term electron (formed from the sun). Baltic ambers were much prized and widely traded in the ancient world. Amber extracts were known to be recommended by Hippocrates of Cos [12]. Amber has a large quantity of succinic acid and the macromolecule biterpenes and trienes that make them naturally aromatic when heated. Recurrent stone formers often used amulets of amber to ward off stone recurrence. One notable exception was Samuel Pepys (1633–1703) who reported in his diary for March of 1665 of his success of the hare's foot amulet he carried to prevent his stones [13]. He wrote that he was "*at a great loss to know whether it be my Hare's foot, or taking every morning of a pill of Turpentine, or my having left off the wearing of a gowne*" [13]. Why would anyone partake of such therapies is clearly reflected in the description of lithotomy by Pepys' friend and colleague John Evelyn observing a surgery in Paris in 1650: "*There was a person of forty years old had a stone taken out of him, bigger than a turkey's egg (Pepys's was the size of a tennis ball): the manner thus: the sick creature was stripped to his shirt, and bound arms and thighs to an high chair, two men holding his shoulders fast down: then the surgeon with a crooked instrument probed til he hit on the stone. He made incision through the scrotum about an inch in length, the he put his forefingers to get the stone as near the orifice of the wound as he could, then with another instrument like a crane's neck he pulled it out with incredible torture to the patient*" [10]. Better pills made of mummy, myrrh, filings of metal, dried hare's dung, and powdered earthworms than the torture of lithotomy.

One more rather bazaar therapeutic alternative, that seems as if it would be a Dark Ages type of treatment, but actually was a Renaissance and Paracelsian addition to medicines therapeutic armamentarium was human blood, urine, and other bodily derived substances [10]. It is nearly impossible for a person today to imagine voluntarily consuming human-derived products for diseases such as bladder or kidney stones or for any malady. But the classic picture is of the epileptic sucking the freshly drawn blood of the gladiator in the arena of Rome. These corpse medicine remedies have been largely overlooked by physicians and historians possibly because of the modern grossness of such regimens [10]. Literally every part of the human body including those of animals and insects was also tried by physicians. This list includes hair, nails, skin, teeth, bodily fluids, and excreta that were all used especially during the Renaissance and into the nineteenth century [10]. The specificity of these corpse-derived therapeutics for stone sufferers is not specifically recorded. However, ground human bladder stones and derived essences of urine were specifically utilized to both treat and prevent stone recurrence.

We have spent much of the Renaissance section previously dealing with the rise of the questioning minds. The simple fact that traditional Galenic medicine had nothing to offer sufferers with urolithiasis was self-evident. The rise of iatrochemists allowed fringe groups in medicine such as surgeons and apothecaries to bridge the gap of respectability. As elite stone sufferers turned to these previously marginalized practitioners, things began to change. Physicians themselves began to become attracted to alchemy and chemistry. Such luminaries as Isaac Newton,

Fig. 10.1 Advertisement for stone disease nostrum (*left*) and the frontispiece from the original 1618 Pharmacopoeia of the Royal College of Physicians of London (*right*)

Robert Boyle, and Robert Hooke began to try previous unheard of therapeutics, many derived from fresh human cadavers, skulls, or blood. Both Boyle and Hooke partook of the cannibalistic ritual of consuming human blood distillates and/or human skull powders. Boyle recommended one "*ancient gentlewoman with morning draughts of her own water*" [10].

Let us pursue the early iatrochemical British physician Thomas Moffet (1553–1604) and Theodore Turquet de Mayerne (1573–1654/1655). Neither of these two early luminaries of medicine contributed directly to our understanding of stone disease, but each contributed mightily to the revolution of therapeutics and to the printing of the 1618 *London Pharmacopoeia* (Fig. 10.1). Dr. Mayerne was a Swiss-born French Protestant who was banned from the faculty of the University of Paris in 1603 for his Paracelsian leanings. He matriculated to London and became the physician to King James I, Charles I, and Charles II as well as many other notable patients. He was above all, intelligent and questioned treatments and sought improved outcomes [14]. He advocated written case histories and the bedside study of disease before Sydenham. Mayerne advocated, however, the liberal use of "corpse" medicines—blood and other human fluids distilled for quintessence of the "vital forces" [14]. Mayerne treated both James I and Charles II with corpse medicines [10]. Thomas Moffet was educated at Trinity College, Cambridge, and studied under John Caius before traveling to the University of Basel where Paracelsus himself taught briefly [15]. Here Moffet studied iatrochemistry of Paracelsus with Felix Platter (1536–1614) and Theodor Zwinger (1533–1588). Moffet and Mayerne were the driving forces in the publication of the *London Pharmacopoeia* [16]. The "art of the drug compounder" was compiled by the Royal College of Physicians as their first standard list of medications and hence therapeutics in England on May 17, 1618; however, it was immediately pulled from circulation due to internal turmoil and for many years was expanded and revised. It is curious that the iatrochemistry of Paracelsus would stimulate a drug compendium which gave the physicians some degree of control over the apothecaries. Moffet, Henry Atkins, and Sir Theodore de Mayerne were all on the committee. The *Pharmacopoeia* was contentious from the outset with old school Galenic classicists battling the new age iatrochemists. Revisions were brought out in 1650, 1677, and 1719. Nicholas Culpeper brought intrigue to the *Pharmacopoeia* by translating it into English in 1649 while attacking the Royalist old guard Royal College of Physicians [17]. Culpeper used his English version to disclose a host of revolting secret concoctions that physicians used including human blood, bones, fat, semen, bile, feces, and urine. Richard Powell (1767–1834) drove a nail into these nefarious therapies. His English translation of the *Pharmacopoeia* in 1809 which he helped revise stated "*although not all the ridiculous, unsavory, or disgusting excerpts were deleted, his edition was a vast improvement over the first edition of 1618*" [18].

John Purcell (1674–1730) was another influential physician who wrote on stone disease in his 1714 "*A Treatise of the Cholick; Containing Analytical Proofs of its many Causes, and Mechanical Explanations of its several Symptoms and Accidents, according to the newest and most rational Principles: Together with its Cure at large*" [19]. He opens right up in his Preface by stating "*Tho' I am satisfy'd no Graduate Physician is ignorant of any of them, yet as the Multitude of Quacks and Pretenders to same Cause, and therefore order the same Medicines for them all…*" [19]. Purcell begins his treatise by attacking Dr. Willis's notions that colic derives from a primary neurologic or nervous condition by presenting evidence that obstruction is the cause of pain. He differentiates different types of colic, renal from biliary and bowel diseases. He then falls back upon the ancient doctrines and practices of Galenic treatment for stone sufferers. But of course, he sarcastically berates those who favor iatrochemical nostrums: "*A Load-stone apply'd to the navel, by which is pretended by Hartmannus that Cholical Pains will immediately cease. Another very expensive Cheat is Water made bitter by the Infusion of a Stone found within a Porcupine, and extoll'd by some as an infallible Remedy*" [19]. He strongly believes in bleeding, purging, and some nonspecific diuretics. He falls back upon classic Galenic methods that had been tried and failed for centuries.

The Rise of Quackery

The events leading to the rising, literate middle class also was associated with the use of printed materials to hawk medications to alleviate whatever was ailing the gullible. But who were the gullible? With no real science possible, literally anyone who suffered from stone disease or knew of someone who suffered from stone disease was likely to believe in almost anything. This included royalty, physicians, the literati, the clergy, and the common man or woman [20]. The common woman is critical to the rise of quackery in our saga of stone disease because the household became the purview of the matriarch, and in some families, the matriarch was the first line of therapy of common diseases, and stone disease was becoming increasingly common. Multiple studies have investigated the use of print media for peddling of quack medicines and nostrums (Fig. 10.1) [21]. Coffee houses were places where print media was read aloud, and for a penny, a cup could be nursed for hours. Advertisements for health care were common in papers and popular magazines, and there is abundant evidence that women were not excluded from coffee houses, and some came to peddle their quack medications. By the end of the seventeenth century, about 25 % of English women were literate, but this number increased to 40 % by 1750 [22]. Medical advertisements shifted to entice the matriarch's and first-line medical decision making, as the careful housewife kept a well-supplied medicine chest with purges, pain-killers, and tonics. Books extolled this particular virtue included "*The Complete Housewife: Or, Accomplish'd Gentlewoman's Companion*" [23]. In 1653, Elizabeth Grey, Countess of Kent, published her famous home medical guide entitled "*A Choice Manual, or Rare Secrets in Physic and Chirurgery*" [24]. This book was a real-world best seller; it went through at least 20 editions. Women were involved in making medicines and taking care of the sick of the family.

There were many imitation books of a similar type, and physicians and others also rushed to the market with practical guides for health-care provision, including John Benjamin Wesley (1703–1791). Wesley was an Anglican cleric who along with his brother Charles founded the modern Methodist movement. His book entitled "*Primitive Physick: or, an Easy and Natural Method of Curing Most Diseases*" was first printed in 1747 [25]. The success of this manual cannot be underappreciated either, for it went through 23 editions in Wesley's own lifetime and was the most successful of anything that he published remaining in print continuously into the 1880s [26]. The established medical profession of course did not stand by quietly as these "non-professional" publications threatened the livelihood of the physician [27]. Dr. William Hawes a physician to the London Dispensary and founder of the Royal Humane Society launched an assault on Wesley's book in 1776 [28]. Wesley in his opening states, "*There have demonstrably shewn, That neither the Knowledge of Astrology, Astronomy, Natural Philosophy, nor even anatomy itself, is absolutely necessary for the quick and effectual Cure for most Diseases incident to Human Bodies: Nor yet any Chymical, or Exotick, or Compound Medicine, but a Single Plant or Fruit duly applied*" [25]. This sentence sums up medicine but perhaps not surgery to this time more eloquently than the author, so I cannot even "*agree to disagree*." For the colicky pain caused by stones, Wesley recommends cold and warm water. In addition, chamomile tea is used with or without decoction (added) mallows. He also recommends the yellow peel of the orange in a glass of water and juniper berries. When bladder pain is bad, he would add an application of hot oats or water over the bladder. For "the gravel," Wesley recommends liberal intake of spinach (now known to be a very high oxalate food source, which should actually increase the risk of new stone formation), the ubiquitous warm water, and peach leave tea. Parsley seed mixed with white wine taken every morning sounds nice. For an obstructed kidney, he falls back to 12 grains of amber dissolved in water. And to prevent stones from forming, he advises to eat a thin slice of whole grain bread every morning. He encourages one to drink a pint of warm water daily just before dinner. Finally, when passing a stone, he believes that a slice of onion placed in warm water aids in passage of the concretion, and it should be taken every 12 h until the pain resolves. In extreme cases, he advises a concoction from ground ivy, radishes, or tar-water [25].

Just to consider how far and how prevalent medical therapy approached quackery itself, one simply has to look at the published literature of the times. Concentrating on English sources for brevity, but these same methods of treatment were by no means limited to England will give the reader some sense of desperation on the eve of chemistry arising as a science. This is protochemistry or pseudotherapeutics, but the intentions of these investigators and practitioners were not simply rapacious. The typical practitioner was not a charlatan looking to make great fortunes with concoctions that did not work. Again we will return to the great Robert Boyle (1627–1691) as an example. Boyle was interested in almost everything that dealt with chemistry. He is considered by many to be the leading light of the early Royal Society, such that even Newton deferred to him [29]. Boyle recruited John Locke into researching the clinical efficacy of blood and blood-derived therapies. Locke's work was thorough and included readings and researches of Helmont and Willis. Locke virtually left experimental and physiologic research after he fell under the influence of the "anti-anatomist" Thomas Sydenham after he left Oxford in 1667 [30]. He henceforward became a radically empirical physician, like Sydenham, and began his fascination with philosophy: "…*whether any thing else is in dispute* *amongst the learned from whose controversy about it are like to arise rather more doubts then any cleare determination of the point & all that anatomy has donne in this case as well as severall others is but to offer new conjectures & fresh matter for endlesse disputations*" [30].

The Paracelsian doctrines for the use of mummies and other human-derived agents closely followed some writings of the German physician Oswald Croll (1563–1609). He wrote quite explicitly about the use of a human corpse: "*Choose the carcass of a red man, whole, clear without blemish, of the age of twenty four years, that hath been hanged, broke upon a wheel, or thrust-through, having been for one day and night exposed to the open air, in a serene time*" [31]. He then dices the cadaver into small pieces, seasons with powder of myrrh and aloes, and repeatedly macerated in spirit of wine. This gruesome concoction was widely utilized for many conditions including stone disease. English Paracelsian physicians rapidly took these new therapeutics. Daniel Border, John French (Boyle's intimate), Christopher Irvine, Edward Bolnest, and George Thomson all adopted all or parts of these prescriptions in treating their patients in England [10]. John French wrote a popular book *The Art of Distillation* in 1651 and describes his own method of preparing oil and water of blood, and for "magistery" (or quintessence) of blood, he states, "*being taken inwardly and applied outwardly, cureth most diseases, and easeth pain*" [32]. His formula for the spirit of urine is described "*the urine of a young man drinking much wine, stood in glass vessels in putrefaction forty days*" and then carefully distilled [32]. Christopher Irvine published his ideas about the use of dead beings to draw off or transfer human illness like magnets in a book *Medica Magnetica* in 1656 [33]. Edward Bolnest also published like-minded ideas and extended the recipe of Crolls's in his *Aurora Chymica* of 1672 [34]. But not all physicians were lured by the new thoughts of the iatrochemists.

Sir Thomas Browne (1605–1682) was a polymath, linguist, antiquarian scholar, natural philosopher, theologian, and bibliophile who wrote about medicine and philosophy in his later life. He was born in Cheapside, London, and the son of a successful merchant. He attended Oxford University and graduated from Pembroke College. He went to the continent and continued his medical studies and eventually received his medical degree from Leiden in 1633 [35]. Browne returned to England and moved to Norwich where he lived and practiced for the rest of his life. His first well-known work was *Religio Medici* that he first privately circulated in 1642. Browne did not write directly about urolithiasis; however, he did make a number of comments in his several literal works about medicine and physicians. In one of his later writings *Hydriotaphia* (1658), he is discussing ancient urn burial rituals. He mentions the ancient Egyptian method of embalming bodies and notes "*all was vanity, feeding the wind, and folly. Egyptian mummies, which Cambyses or Time hath spared, avarice now consumeth. Mummy is become merchandise, Mizraim cures wounds, and Pharaoh is sold balsams*" [36]. Browne is lampooning the notion that mummy's bodies or medicines derived from such sources do any good except to those selling them. He backhandedly is deriding those, including his colleagues, who utilize such therapies.

Sir Thomas Browne treated the wealthy as well as the poor of Norwich, which was the second largest city in England. He most likely consulted on the case of Sir Thomas Adams of Spixworth who suffered from bladder stones [37]. Adams's marble tomb at St. Mary and St. Margaret's Church reads in Latin "*after he completed his eighty-first year and borne with invincible patience the acute pain of the stone- which surpassed twenty-five [apothecary or 852 grams] ounces in weight he was freed from the burdens of life on 24 Feb. 1667*" [37]. Sir Thomas Adams's stone was removed posthumously and was kept by the family until 1869 when it was presented to St. Thomas's Hospital for their museum. Browne would also treat Sir Hamon L'Estrange of Hunstanton as well as two bishops of Norwich, Joseph Hall and Anthony Sparrow. These bishops in turn helped fund care for 32 poor sufferers with bladder stones that underwent lithotomy during this era [37]. Medically, Browne resisted the Paracelsian "corpse medicines" as well as bleedings.

Instead, Browne's therapeutic recommendations included "Tunbridge wells water" or Epsam as well as dietary advice. He prescribed extracts of marshmallow, white water lily, cumfrey, and almond milk. He was asked to advise upon the final illness of Sir Edward Walpole (grandfather of the prime minister who we'll discuss later) who also suffered from bladder stones. He advised against the use of "Goddard's Dropps" which had become the skull medicine of Charles II: [10] "*Dr. Browne and all his other Phisitions was very much against his taking the Dropps and he himself was not of opinion they could do him good till the Lord Townshend advised him to take them*" [37].

Browne did have a rather poor opinion of most surgeons in his time at Norwich. In 1679 he wrote, "*The ignorance of chirurgeons as to the chirurgical operations creates so many mountebanks and stage quack-salvers*" [37]. Yet his two bishop patients did readily fund lithotomies by John Hubbard, Miles Mayhew, William Rayby, and Gutteridge and son upon the poor of Norwich. Browne did encourage his son Edward during his postgraduate work in Paris to study and learn lithotomy: "*I am glad you have seen more cutte for the stone and of different sex and ages. If opportunitie serveth you doe well to see more, wch will make you well experienced on that great operation and almost able to performe it your self upon necessite and where none could do it. Take good notice of their instruments, and least make such a draught there of, and especially of the dilator and director, that you may hereafter well remember it and have one made by it*" [37]. At this time, the older Marian lithotomy was widely utilized in Paris, but alas Edward followed his father into medicine and never did practice surgery.

A postscript on Browne will wrap up his part in this history; he famously wondered "*who knows the fate of his bones, or how often he is to be buried?*" [36] He anticipates all too poignantly his own burial desecration and his skull's resurrection: "*To be gnawed out of our graves, to have our skulls made drinking-bowls, and our bones turned into pipes to delight and sport our enemies, are tragical abominations*" [36]. In 1840, workers digging a grave at St. Peter Mancroft Church unwittingly opened the vault of Sir Thomas Browne's body. The brass plaque on his coffin lid had been split and the diggers notified the sexton, George Potter. Dr. Robert Fitch a chemist, druggist, and amateur was called in to record the findings of the exhumed body of the famous Norwich physician. The epitaph written on the broken plaque read "*Hoc Loculo indormiens, Corporis Spagyrici pulvere plumbum in aurum Convertit*" (Sleeping in this coffin, by the dust of his alchemical body, he converts lead into gold) [38]. Browne's earthly remains were re-interred except Potter, later christened "Skull George," sold the skull to Dr. Edward Lubbock for an unrecorded sum. He in turn gave the skull to the Norfolk Hospital Museum where a young surgeon (a lithotomist ironically) who would become interested in the legacy of Sir Thomas Browne, Charles Williams, began to investigate the skull intensely. In 1848, the Norwich Pathologic Society was formed, and its members met quarterly in the Norwich and Norfolk Hospital Museum, joined in that year by the skull of past member, Sir Thomas Browne. In 1851 the Norfolk and Norwich Hospital Museum formally put on display its hundreds of calculi for which the institution had rightfully become famous. It is only fitting that the patron saint of the hospital Sir Thomas Browne's skull should join the shelves as a prized possession next to the stones that made the institution famous.

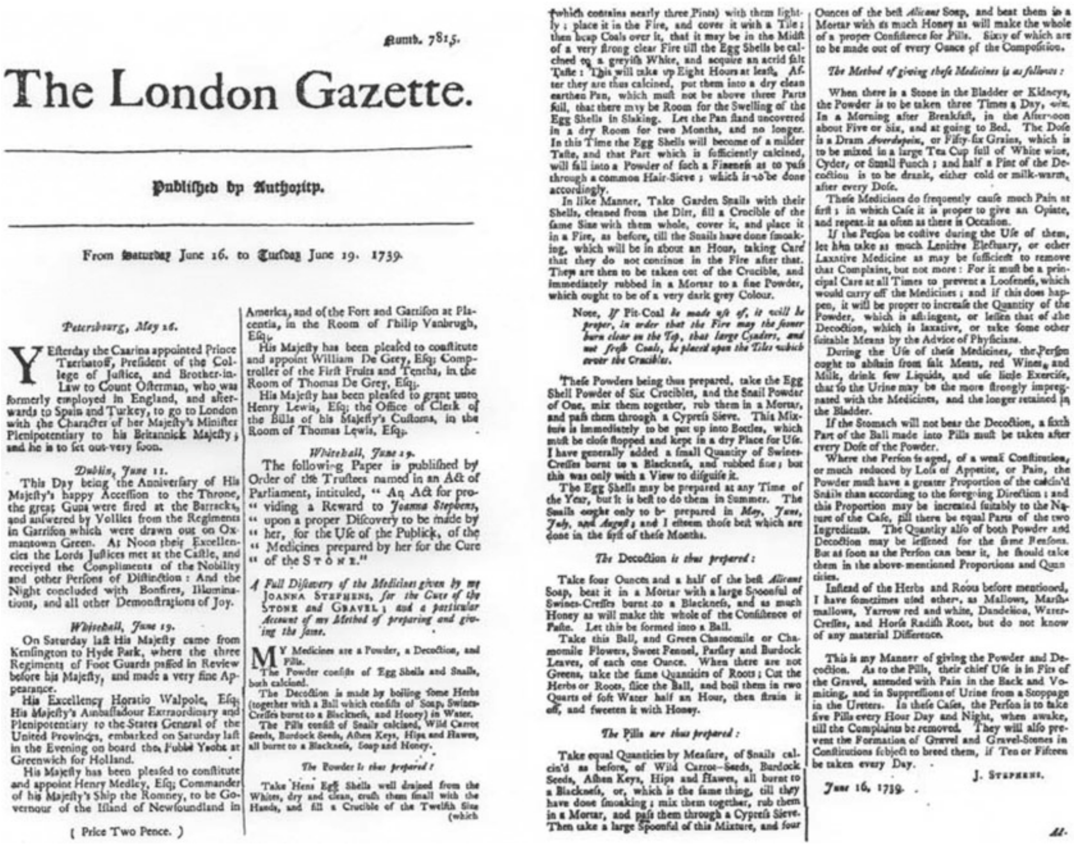
The Romans perhaps were the first to really popularize natural springs for their healing potential. Some types of springs, such as thermal springs, had high mineral contents and were recommended for both submersion and consumption. Sir John Floyer published a book on "*Psychrolousia: The History of Cold Bathing, Both Ancient and Modern*" in 1720. This book popularized visitations at beaches and cold springs [39]. J.S. Hahn followed with another treatise, and finally Dr. James Currie published his "*Medical Reports on the Effects of Water, Cold and Warm, as a remedy in Fevers and Other Diseases*" in 1797 [40]. Many locations developed some notoriety for the quality of the thermal springs in particular, which attracted stone sufferers like the relics of the saints in the Dark Ages.

Ludwig van Beethoven (1770–1827) suffered from recurrent bouts of colic between writing masterpieces of music that literally transformed music. From 1805 till his death, Beethoven suffered as stone patients can. In the first half of 1825, Beethoven wrote a String Quartet in A Minor, Opus 132. During this period, he suffered an unusually intense and painful episode of "colic." The second movement is a mystical and intense piece of music. On it Beethoven wrote the following inscription: "*Heiliger Dankgesang eines Genesenen an die Gottheit, in der lydischen Tonart*" (Holy song of Thanksgiving to the Deity from one who has been cured in the Lydian mode) [41]. Beethoven did what Michel Montaigne did previously; he visited thermal spas and partook hydrotherapies and natural spring waters. He did improve from time to time but suffered recurrent bouts of colic. In 1970, Dr. Karl Portele discovered the original autopsy documents in the Vienna Museum of Anatomical Pathology. Beethoven's kidneys were in fact removed and opened. The final entry of the autopsy findings is particularly significant: "*Both kidneys were pale red in color and when opened out the cellular texture measured the length of the terminal phalanx of the thumb, it was covered with a dark turbid fluid which obscured the view. Every single calyx was filled with a calcareous concretion like a pea which had been cut across the middle*" [42].

Throughout the era from the end of the Renaissance through the end of the eighteenth century, numerous methods were tried in lieu of the classic Galenic regimens that had been used for centuries prior to aid the stone sufferer. These nostrums were often desperate attempts to do something for these patients who were plentiful and suffered mightily. The chief apothecary to the Sun King, Louis XIV, was Pierre Pomet (1658–1699) who wrote extensively about therapeutics. In 1694 he published his "*Complete History of Drugs*" which proved to be a popular reading material [43]. He hypothesizes on the methods of some medications, such as mummy that capture the "vital spirits" of the dead. He discusses transference of illness to animals, which explains why a pigeon might be split open and applied to the flank of a stone sufferer. He does not mention the rising notion of advertising remedies, however, which increased dramatically in the seventeenth century. For instance, one add run in the Whitehall Evening Post on December 19, 1749, offered "*by the King's Royal Letters Patent, Schwanberg's Liquid Shell for a sure dissolvement for stone and gravel*" [44]. This common nostrum was also investigated by Stephen Hales and who experimented on this substance. He noted no dissolution of stones but that the medication produced a white precipitate in people's urine that suggested that the medication was doing something, but it certainly did not dissolve any stone. Finally, before turning to the central character of this chapter, Antoine Fourcroy, a rising chemistry superstar from France, clarified for the pharmaceutical industry that human fat could be distilled and made easier for human consumption (we will meet him again in Founding Fathers) [10].

Joanna Stephens' Controversy

In the early parts of the eighteenth century, the incidence of stone disease had become significant enough that a public outcry began to force those in public office to pay particular attention to stone disease. This should be kept in mind as the rise above and beyond the knowledge of the Ancients progressed. It is difficult to ascertain how these people, enthralled with experiment and attainment of new information, could have equally been smitten with quack remedies. It is this era that Mrs. Stephens rose to fame because of her abilities to concoct remedies that would dissolve stones, among many of her known nostrums [45]. Members of the public were rabidly in favor of acquiring her lithotriptic preparation for "*distemper of the stone*." Sufferers of stone disease, their families, and friends were all aroused to raise a fund of not less than £5,000 as a reward for anyone who could find a solvent for the stone [46]. Obviously this enormous sum brought Mrs. Stephens to produce her best solvent to the competition, and she was required to give the "secret" ingredients to the panel commissioned to investigate her cure. In an Act of the



Numb. 7815.

The London Gazette.

Publish'd by Authority.

From Saturday June 16. to Tuesday June 19. 1739.

Petersbourg, May 26.

YEsterday the Czarina appointed Prince Tzerbatoff, President of the College of Justice, and Brother-in-Law to Count Osterman, who was formerly employed in England, and afterwards to Spain and Turkey, to go to London with the Character of her Majesty's Minister Plenipotentiary to his Britannick Majesty; and he is to set out very soon.

Dublin, June 11.

This Day being the Anniversary of His Majesty's happy Accession to the Throne, the great Guns were fired at the Barracks, and answered by Vollies from the Regiments in Garrison which were drawn out on Oxmantown Green. At Noon their Excellencies the Lords Justices met at the Castle, and received the Compliments of the Nobility and other Persons of Distinction: And the Night concluded with Bonfires, Illuminations, and all other Demonstrations of Joy.

Whitehall, June 19.

On Saturday last His Majesty came from Kensington to Hyde Park, where the three Regiments of Foot Guards passed in Review before his Majesty, and made a very fine Appearance.

His Excellency Horatio Walpole, Esq; His Majesty's Ambassadour Extraordinary and Plenipotentiary to the States General of the United Provinces, embarked on Saturday last in the Evening on board the Fubbs Yacht at Greenwich for Holland.

His Majesty has been pleased to constitute and appoint Henry Medley, Esq; Commander of his Majesty's Ship the Romney, to be Governour of the Island of Newfoundland in America, and of the Fort and Garrison at Placentia, in the Room of Philip Vanbrugh, Esq;

His Majesty has been pleased to constitute and appoint William De Grey, Esq; Comptroller of the First Fruits and Tenths, in the Room of Thomas De Grey, Esq;

His Majesty has been pleased to grant unto Henry Lewis, Esq; the Office of Clerk of the Bills of his Majesty's Customs, in the Room of Thomas Lewis, Esq;

(Price Two Pence.)

Whitehall, June 19.

The following Paper is published by Order of the Trustees named in an Act of Parliament, intituled, "An Act for providing a Reward to *Joanna Stephens*, upon a proper Discovery to be made by her, for the Use of the Publick, of the Medicines prepared by her for the Cure of the STONE."

A Full Discovery of the Medicines given by me JOANNA STEPHENS, *for the Cure of the* STONE *and* GRAVEL; *and a particular Account of my Method of preparing and giving the same.*

MY Medicines are a Powder, a Decoction, and Pills.

The Powder consists of Egg Shells and Snails, both calcined.

The Decoction is made by boiling some Herbs (together with a Ball which consists of Soap, Swines-Cresses burnt to a Blackness, and Honey) in Water.

The Pills consist of Snails calcined, Wild Carrot Seeds, Burdock Seeds, Ashen Keys, Hips and Hawes, all burnt to a Blackness, Soap and Honey.

The Powder is thus prepared:

Take Hens Egg Shells well drained from the Whites, dry and clean, crush them small with the Hands, and fill a Crucible of the Twelfth Size (which contains nearly three Pints) with them lightly; place it in the Fire, and cover it with a Tile; then heap Coals over it, that it may be in the Midst of a very strong clear Fire till the Egg Shells be calcined to a greyish White, and acquire an acrid salt Taste: This will take up Eight Hours at least. After they are thus calcined, put them into a dry clean earthen Pan, which must not be above three Parts full, that there may be Room for the Swelling of the Egg Shells in Slaking. Let the Pan stand uncovered in a dry Room for two Months, and no longer. In this Time the Egg Shells will become of a milder Taste, and that Part which is sufficiently calcined, will fall into a Powder of such a Fineness as to pass through a common Hair-Sieve; which is to be done accordingly.

In like Manner, Take Garden Snails with their Shells, cleaned from the Dirt, fill a Crucible of the same Size with them whole, cover it, and place it in a Fire, as before, till the Snails have done smoaking, which will be in about an Hour, taking Care that they do not continue in the Fire after that. They are then to be taken out of the Crucible, and immediately rubbed in a Mortar to a fine Powder, which ought to be of a very dark grey Colour.

Note, *If* Pit-Coal *be made use of, it will be proper, in order that the Fire may the sooner burn clear on the Top, that large Cynders, and not fresh Coals, be placed upon the Tiles which cover the Crucibles.*

These Powders being thus prepared, take the Egg Shell Powder of Six Crucibles, and the Snail Powder of One, mix them together, rub them in a Mortar, and pass them through a Cypress Sieve. This Mixture is immediately to be put up into Bottles, which must be close stopped and kept in a dry Place for Use. I have generally added a small Quantity of Swines-Cresses burnt to a Blackness, and rubbed fine; but this was only with a View to disguise it.

The Egg Shells may be prepared at any Time of the Year, but it is best to do them in Summer. The Snails ought only to be prepared in *May, June, July, and August*; and I esteem those best which are done in the first of these Months.

The Decoction is thus prepared:

Take four Ounces and a half of the best *Alicant* Soap, beat it in a Mortar with a large Spoonful of Swines-Cresses burnt to a Blackness, and as much Honey as will make the whole of the Consistence of Paste. Let this be formed into a Ball.

Take this Ball, and Green Chamomile or Chamomile Flowers, Sweet Fennel, Parsley and Burdock Leaves, of each one Ounce. When there are not Greens, take the same Quantities of Roots; Cut the Herbs or Roots, slice the Ball, and boil them in two Quarts of soft Water half an Hour, then strain it off, and sweeten it with Honey.

The Pills are thus prepared:

Take equal Quantities by Measure, of Snails calcin'd as before, of Wild Carrot-Seeds, Burdock Seeds, Ashen Keys, Hips and Hawes, all burnt to a Blackness, or, which is the same thing, till they have done smoaking; mix them together, rub them in a Mortar, and pass them through a Cypress Sieve. Then take a large Spoonful of this Mixture, and four Ounces of the best *Alicant* Soap, and beat them in a Mortar with as much Honey as will make the whole of a proper Consistence for Pills. Sixty of which are to be made out of every Ounce of the Composition.

The Method of giving these Medicines is as follows:

When there is a Stone in the Bladder or Kidneys, the Powder is to be taken three Times a Day, viz. In a Morning after Breakfast, in the Afternoon about Five or Six, and at going to Bed. The Dose is a Dram *Averdupois*, or Fifty-six Grains, which is to be mixed in a large Tea Cup full of White wine, Cyder, or Small Punch; and half a Pint of the Decoction is to be drank, either cold or milk-warm, after every Dose.

These Medicines do frequently cause much Pain at first; in which Case it is proper to give an Opiate, and repeat it as often as there is Occasion.

If the Person be costive during the Use of them, let him take as much Lenitive Electuary, or other Laxative Medicine as may be sufficient to remove that Complaint, but not more: For it must be a principal Care at all Times to prevent a Looseness, which would carry off the Medicines; and if this does happen, it will be proper to increase the Quantity of the Powder, which is astringent, or lessen that of the Decoction, which is laxative, or take some other suitable Means by the Advice of Physicians.

During the Use of these Medicines, the Person ought to abstain from salt Meats, red Wines, and Milk, drink few Liquids, and use little Exercise, that so the Urine may be the more strongly impregnated with the Medicines, and the longer retained in the Bladder.

If the Stomach will not bear the Decoction, a sixth Part of the Ball made into Pills must be taken after every Dose of the Powder.

Where the Person is aged, of a weak Constitution, or much reduced by Loss of Appetite, or Pain, the Powder must have a greater Proportion of the calcin'd Snails than according to the foregoing Directions; and this Proportion may be increased suitably to the Nature of the Case, till there be equal Parts of the two Ingredients. The Quantity also of both Powder and Decoction may be lessened for the same Persons. But as soon as the Person can bear it, he should take them in the above-mentioned Proportions and Quantities.

Instead of the Herbs and Roots before mentioned, I have sometimes used others, as Mallows, Marshmallows, Yarrow red and white, Dandelion, Water-Cresses, and Horse Radish Root, but do not know of any material Difference.

This is my Manner of giving the Powder and Decoction. As to the Pills, their chief Use is in Fits of the Gravel, attended with Pain in the Back and Vomiting, and in Suppressions of Urine from a Stoppage in the Ureters. In these Cases, the Person is to take five Pills every Hour Day and Night, when awake, till the Complaints be removed. They will also prevent the Formation of Gravel and Gravel-Stones in Constitutions subject to breed them, if Ten or Fifteen be taken every Day.

J. STEPHENS.

June 16, 1739.

At-

Fig. 10.2 Joanna Stephens' famous add in the London Gazette, June 16, 1739

Parliament, Mrs. Joanna Stephens received the Royal Assent on June 14, 1739, entitled "*An Act providing a reward to Joanna Stephens upon a proper discovery to be made by her for the use of the Publick of medicines prepared by her for the cure of stone*" [47] (Fig. 10.2).

The assessors of the award were to be His Grace John Lord Archbishop of Canterbury, the Right Honourable Philip Lord Hardwicke, Lord High Chancellor of Great Britain, the Right Honourable Spencer Earl of Wilmington, Lord President of the Council, and the Lord Privy Seal, with 28 other prelates, peers, and commoners. These included two fellows of the Royal Society; five physicians, including Thomas Pellett, president of the Royal College of Physicians; and three surgeons William Cheselden, Caesar Hawkins, and Samuel Sharp [47]. The Archbishop of Canterbury who had the secret recipe and its compounding revealed to him gave us her statement as follows: "*The Powder consists of egg-shells and garden snails well calcined until the snails have done smoking. The decoction was made by boiling various herbs with soap, honey and swine-cresses burnt to blackness. The Pills were composed of calcined snails, wild carrot seeds, burdock seeds, ashen keys, hips and haws, all burnt to a blackness, soap and honey*" [48].

The inquiry in the efficaciousness of Mrs. Stephens' nostrum ended on March 5, 1740, with the recommendation of awarding her the full award of £5,000. Reverend Stephen Hales was one of those "commoners" on the panel to investigate the claims of Mrs. Stephens [49]. In addition, two French chemists of the Academie Royale des sciences were C.F. Geoffroy and S.F.

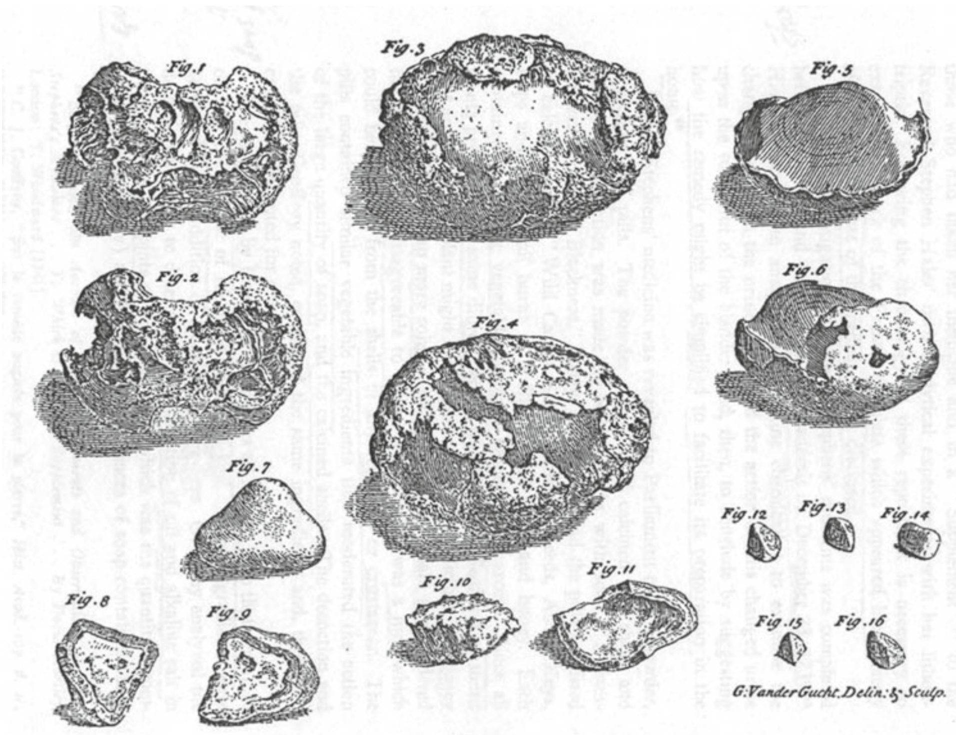


Fig. 10.3 The dissolution of stones in vitro according to David Harley [51]

Morand [50]. Finally David Hartley who was also a fellow of the Royal Society independently assessed Mrs. Stephens' recipe on stones and in patients (Fig. 10.3) [51].

Inquiry into Stephens' Nostrums

The Reverend Stephen Hales and the Chemist Joseph Black were all intrigued by the magical potential of the Stevens lithotriptic. In London, the "skeptical chymist" Boyle was likewise fascinated. Hales isolated the lime as the active ingredient and had the foresight to suggest "*Does the fact that soap-lye dissolves stones in vitro mean that it will be an effective dissolvent in vivo?*" He published his studies which were presented with David Hartley's observations [52].

The clinical trial included four patients treated with the medicine. They actually tried to control who was chosen, and tried to keep all other variables as similar as possible. Each patient was sounded by one of the surgeons to determine the presence of a bladder stone. Each patient received the medicines as prescribed and was observed [53]. Each patient passed stone fragments and copious white mucus in the urine and each of the four patients were subjectively greatly relieved of their suffering. Each patient was sounded again at the conclusion of the therapy and no further stones were noted. These investigations were all sworn officially to the accessors. There were problems of course. First David Hartley the physician in charge also had stone disease and had successfully used Mrs. Stephens' medicine so he was biased. Also, Lord Walpole happened to be the prime minister to two monarchs was also involved, and he too swore to the efficacy of Mrs. Stephens' medicine for he too suffered from bladder stones and had successfully been treated. All in all, the studies though attempting to be fair were in fact biased. Stephen Hales must have felt undue pressure to find some efficacy in his in vitro studies with stones [49]. Finally, Lord Walpole died on March 18, 1745, and had requested an autopsy for scientific purposes.

It would be appropriate now to finish the saga of the Walpole family in this tale of quackery at this point. It began with our discussion of the medical opinion of Sir Thomas Browne against the use of the King's Dropps to treat the grandfather, Sir Edward Walpole [37]. The First Earl of Orford, formerly Sir Robert Walpole (1678–1745), and former prime minister to two kings would generate a maelstrom of medical and surgical interest when he suffered from bladder stones. James Jurin (1684–1750), physician to Guy's Hospital and president of the Royal College of Physicians of London, introduced his *lixivium lithontrypticon* which also contained soap-lye and with which he gained a great reputation. He was called in to consult on Walpole by John Ranby (1704–1773), a leading London surgeon and sergeant-surgeon to King George II. Jurin's *lixivium lithontrypticon* did little to ease the suffering of Walpole, and he died soon after on March 18, 1745 [54]. The Earl of Orford made specific instructions with Ranby that should he perish he wanted a full account of his case, including autopsy findings so "*that Mankind might reap the proper benefit from a Relation of that Nature, and Physicians be deterr'd for the future from enterprising with such Edged-Tools, as in his opinion, was the Lithontropic Lixivium*" [54]. Ranby diligently published his monograph recording the history of the former prime minister's illness with autopsy findings of severe cystitis, "*prostate glands were enlarged and harder than they commonly are with about thirty small bladder stones*" [55]. Three years later, the Right Honorable Horatio Walpole, son of Robert, also developed bladder stones and presented his own case history and treatment by his friend and physician, Lord Harrington, using the limewater introduced by Robert Whytt (1714–1766 whom we'll meet in a later chapter) [53]. It should be a fitting conclusion of the Walpole clan that the Walpoles noted ironically that their mother too suffered from bladder stones.

Another Fish Tale: Modern Chemolysis

Lest the reader believe that the modern attempts to rid a patient suffering from stone disease has lost all of the colorful past traditions that we have thus far pondered, let us pursue the history and current status of modern lithotriptics, under the guise of chemolysis. The ancient notion to restore to solution the concretions that have precipitated seems like a reasonable modern capability with current chemical knowledge. Sadly, this too has evolved and involves our attentions turning momentarily to a truly remote geographical region and a macabre chapter in the history of medicine that involves the only vertebrate parasitic infestations of humans, a catfish.

The Candirú is a small parasitic catfish that belong to the order of catfishes (Siluriformes) and family (Trichomycteridae) with over 136 species: "*Throughout the Amazon valley for more than a hundred years, the tale has been told of a fish that has the uncanny habit of penetrating the urethra of men and women bathers, particularly if they should pass urine while in the water*" [56]. It is the subfamily Vandelliinae that are the blood parasites known as the candirús. This fish has been scientifically documented, and case reports of human parasitization by this fish are widely known, with the most famous dramatization being on season 3, episode 21, of Grey's Anatomy called "*Desire*" which aired on April 26, 1907 [57]. The fish and its human attraction prompted the natives around the Amazon basin to develop innovative methods of dealing with this in endemic areas. They constrict the prepuce with strings and sometimes wear a small coconut shell and various other genital protectors called "*inobá*" which are dried palm leaves for men or modified bark "*uluri*" for women. If, however, a fish finds a human host, the natives used fresh juice called Xagua as the surest method of killing the beast and dissolving its skeleton [58, 59]. A Dr. Bach described in the late 1800s that "*the unripe jaguar fruit is the standard treatment of dislodging the* ***canero*** *once it has attacked. The centers of the smaller green fruits are scraped out,* *mashed and squeezed, and mixed with water, the strength of preparation varying considerably. In a comparatively short time, varying from a few minutes to about two hours, according to natives, the fish is dislodged.*" Vinton and Strickler recorded another successful treatment with the fruit drink but claimed it was an "*unpalatable medicine*" [60].

This fruit, the buitach apple (*Genipa americana*) used to help dissolve and dislodge this pesky fish, was investigated and synthesized by Dr. Lin who noted the high citric acid levels, and he tried to dissolve bladder stones [61]. Crowell had already attempted to dissolve a cystine stone in a kidney by retrogradely lavaging mercurochrome every other day in 1924 [62]. Hellstrom also reported an attempt to dissolve an infectious-type stone using a 1 % phosphoric acid, boric acid, and potassium permanganate to acidify the urine in his patient in 1938 [63]. The following year, Fuller Albright and his team at Massachusetts General Hospital tried to dissolve calcium phosphate bladder stones using isotonic citrate solutions (the catfish cure). This is a landmark event in stone disease; the Albright team became the first multispecialty and interdisciplinary group to focus on stone disease [64]. 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 urologist Howard Ingram Suby (1909–1974) who worked in the lab to develop better solutions with less irritability to the urinary mucosa and quicker dissolution times [65]. A whole series of chemicals were tried in animal models with the development of Suby's M and G solutions. Howard Suby's G solution (isotonic citrate, magnesium oxide, and sodium carbonate) became the first effective nonsurgical alternative to phosphatic stone dissolution therapy. By 1955, the Guardian Chemical Corporation was approached by Dr. William P. Mulvaney, a urologist at the University of Cincinnati, and a chemical solvent used to unclog milk pasteurizing equipment, similar to Suby's G solution but containing malonic and gluconic acid, was investigated. Dr. Alfred E. Globus of the Guardian Co. called this hemiacidrin and named it Renacidin®. This was effective for dissolving struvite stones. The first in vitro study was performed by Mulvaney in 1959 on 50 human stones and 3 in vivo human trials [66].

Renacidin 10 % solution became widely utilized for treating encrusted Foley catheters and struvite stone disease through the early 1960s. But problems quickly ensued including six reported deaths investigated by the Food and Drug Administration which banned the use on June 13, 1963 [67]. The problems were in difficulty delivering and monitoring patients using 10% Renacidin. The chemical was typically infused through small tubes placed in the urinary tract under pressure. The high levels of magnesium could be absorbed systemically which could cause cardiac irritability, papillary necrosis, and cerebral edema. In addition, struvite stones are infected and problems with septic complications limited use. The final hurdle was the prolonged time necessary to dissolve large stones, especially staghorn renal stones [67].

Renacidin is not completely forgotten nor is dissolution therapy. Despite the plethora of problems with these types of therapies, complicated patients still sometimes will benefit from consideration of these modalities. Sales of Renacidin from United-Guardian, Inc. still range from $1.2 to 1.5 million annually [68]. Also the basic science of stone chemistry has continued to advance, and research into dissolution therapy is far from over. One recent investigation compared in vitro six different solvents for the dissolution of phosphate-containing calculi. The authors did find that newer chelating agents are possible to increase the dissolution rates without significantly increasing the risk of toxicity of the solutions [68].

Conclusions

> "*There are Many cured of Diseases by the Imagination only; for Nature often submits to the Thoughts and vehement Desires of the Soul and, our Spirits being affected, the Body is affected also.*"
>
> John Greenfield (1710, A Compleat Treatise on the Stone and Gravel)

With the physicians interested in truly helping patients suffering from the horrors of urinary stone disease, they were literally trapped between a "rock and a hard place." Knowledge, especially scientific, was on the rise. Yet the physiology regarding the formation and types of stone disease would have to wait for the next generation. Stone disease was still trapped in the darkness of lack of adequate knowledge as to the various stone types and the conditions that led to stone formation. The medical treatment prior to this era consisted of botanicals such as cassia, crocus, myrrh, cinnamon, the seeds of sessile, maidenhair fern, the root of laurel, marshmallow, and the mineral amber with its derivatives. Others recommended baths, poultices, heat, cupping, bleeding, and purges (either vomiting or enemas). There were those that truly believed in the essence of goat's blood, mashed millipedes, and pickled or roasted sparrow. The uses of animal and human corpse remedies were tabulated by Johann Schröder in his *History of Animals as they are Useful in Physic and Chirgery* [5]. The writings about Joanna Stephens and the perpetration of a massive hoax upon the British government are widely disseminated but historically incorrect [45]. The people involved with this early attempt at chemolysis were just desperately trying to develop a method to humanely treat those suffering with this increasingly common condition. They rigorously tried to investigate Mrs. Stephens' nostrums with the primitive chemistry of the times. The four patients in the preliminary trial were heroic volunteers. One can almost imagine the suffering endured by these four patients being sounded with rigid instruments by the surgeons prior to undergoing treatment with Stephens' powders and pills, but they all had to endure it again following the completion of the regimen. Dr. David Harley and Lord Walpole have also been cited variously for being too intimately involved in the process since both suffered personally from stones and both "supposedly" benefited from Mrs. Stephens' medicines. Walpole eventually had an autopsy at his own request, and stones were still present within his bladder, ultimately proving the failure of Mrs. Stephens' cure. Walpole is estimated to have consumed "*nearly two hundred-weight of soap and the equivalent of 1,200 gallons of lime-water*" through his life, quite a price to pay for proving his point [55]. In retrospect this would seem to be true, but in actuality, adequate scientific trials with rigorous controls did not yet exist. Their own personal suffering seemed to be lessened by her cures so how could they be so vilified even during her remaining life. A modern attempt to understand Mrs. Stephens and her phenomenal financial success and what eventually became of her is now all but impossible. Attempts to find what happened to this enigmatic medical provider have failed [55]. She probably died and was buried inconspicuously in her local parish, but we can be assured that she was probably not resurrected for "corpse medicine" like many in England, France, Germany, and Italy.

There is one more stone, left metaphorically unturned that fits into this discussion of therapeutics that has been saved until the very end of this chapter. Has anyone ever investigated the use of prayer, singly or in multiple to help those suffering from stone disease? The answer is no; however, there are two historical investigations that deserve mention. But first, to whom should one pray and what should one pray for? Before going into this highly contentious area, there is a Roman Catholic patron saint or two for sufferers of kidney stones, bladder stones, and colic [69]. St. Aelred of Rievaulx was born in Hexham, England, in 1110 C.E. (current era). He originally was at the court of King David I of Scotland prior to becoming a monk at age 24 (1134 C.E.). Aelred was quite scholarly and wrote several ecclesiastic and historical works. He appears to have suffered horribly from stone disease himself, so it is natural that one might pray to him for intercession. There is also Saint Alban of Mainz who was beheaded and became a martyr in 406 C.E. executed by the Goths. He is often depicted carrying his own head in his hands. Just how he became a patron saint for kidney stones has never been justifiably been documented. Finally, there is St. Liborius of Le Mans [70]. Little is known of him; he was a Gaul (early French) and influenced the growth of the early Roman Catholic Church. It is believed that he died in the arms of his friend

Martin of Tours and is depicted as a bishop carrying small stones on a book. He has become the saint most often called upon by those suffering colic and stone disease [71]. Liborius has been called the patron saint of European urology.

Now let's turn to evidence against the efficacy of divine intervention. The first comes from Charles Darwin's cousin, Francis Galton. Galton performed an absolutely stunning piece of statistical wizardry and reported on the "*Statistical Inquiries into the Efficacy of Prayer*" in the Fortnightly Review in 1872. He begins his treatise with the following sentence: "*An eminent authority has recently published a challenge to test the efficacy of prayer by actual experiment. I have been induced, through reading this to prepare the following memoir for publication…*" [72]. He proceeds to take church arguments on the effectiveness and use of prayer, especially for intercession and develops a strategy to investigate claims on efficacy. He utilizes statistics taken from Dr. Guy published in the Journal of the Statistical Society which compares members of royal houses, clergy, lawyers, medical professionals, English aristocracy, gentry, trade and commerce, officers of the Royal Navy, English literature and science, officers in the Army, and Fine Arts. The Sovereigns listed have the shortest lives of all those of affluence despite the fact that they are the most often the object of intercessional praying. Of the three professionals (clergy, lawyers, and medical men), the clergy are the soonest to die suggesting "*the prayers of the clergy for protection against the perils and dangers of the night, for protection during the day, and for recovery from sickness, appear to be futile in result.*" Galton continues to site example after example and gets to gist of his argument, "*First, if it is proved that God does not answer one large class of prayers at all, it would be of less importance to pursue the inquiry. Secondly, the modern feeling of this country is so opposed to a belief in the occasional suspension of the general laws of nature, that an English reader would merely smile at such an investigation*" [72]. Is Galton developing the satire of Swift? The second study is much more modern and concerns contemporary recovery from coronary artery bypass graft (CABG). This was a multi-institutional (6) randomized prospective trial to investigate the ability of intercessory prayer to improve outcomes. Between January 1998 and November 2000, 1,802 patients were randomized into three groups: uncertain IP (group 1), uncertain no IP (group 2), and certain IP (group 3). Intercessory prayer had no effect on complication-free recovery from CABG, and incidentally, it confirmed some of the findings of Galton [73]. Those patients receiving intercessory prayer had higher numbers of complications. Personally, sarcasm or cynicism aside, if displaced back in time, the author would choose none of the above, but rather oenodotes and oenotherapy—bring on the wine! [74]

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11 Evolution of Stone Disease

Introduction

Stones are a heterogeneous group of biomaterials that crystallize in the urine or cellular interstices. As they grow, they might also disrupt normal physiology and function of the urinary tract. This raises the question: Are these concretions a normal variation in the development and function of the urinary tract? A whole literature has evolved similar to the history of evolution itself. How this all links again to the history of knowledge about the natural world that occurred during the seventeenth and eighteenth centuries is the purpose of this chapter. Here our focus concerns two new sciences, biology and chemistry, that existed under the mantra of "natural philosophy" but were irreversibly altered in the wake of Copernicus, Vesalius, Galileo, and Harvey leading to the paradigm-shift-producing work of Isaac Newton.

The 1573 work of Ambroise Paré "*Des Monstres et Prodiges*" began the insightful questioning of biology [1, 2]. Cardan, Fernel, and Paracelsus tried also to probe biology further; they again lacked the necessary physiology. Harvey also tried to follow his monumental observations and experimentation on the circulation of blood by attempting to similarly understand fertilization and gestation but lacked both the tools and the great foresight to make another stunning advancement. Even Montaigne wondered about the complexity of biology, "*What a wonderful thing it is that that drop of seed from which we are produced bears in itself the impressions, not only of the bodily shape, but of the thoughts and inclinations of our fathers! Where can that drop of fluid harbor such an infinite number of forms? And how do they convey those resemblances, so heedless and irregular in their progress, that the great-grandson shall be like his great-grandfather, the nephew like his uncle*?" [3]. This is speculation indeed by this gifted savant with perhaps a hint of irony knowing that his father suffered mercilessly from stone disease and knowing that he, too, harbored these concretions.

Galileo presciently noted that "*Philosophy is written in a great book which is always open before our eyes, but we cannot understand it without first applying ourselves to understanding the language and learning the characters used for writing it*" [4]. He also would suffer from the stone but opened the doors for Descartes to follow: "*If we wish to make out some writing in which the meaning is disguised by the use of a cipher, though the order here fails to present itself, we yet make up an imaginary one, for the purpose both of testing all the conjectures we may make about single letters, words or sentences, and in order to arrange them so that when we sum them up we shall be able to tell all the inferences that we can deduce from them*" [5]. This is an apt metaphor for knowledge of stone physiology to date. Leibnitz too followed this train of thought and commented "*The art of discovering the causes of phenomena, or true hypotheses, is like the art of deciphering, in which an ingenious conjecture often greatly shortens the road*" [6]. Biology, medicine, and physiology (medicine's child)

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were all beginning to develop during this time, and stone disease was an obvious problem that could be evaluated.

Literally at the end of the eighteenth century, the ancient classification of the three kingdoms of nature (animal, vegetable, and mineral) gave way to a two-system arrangement noted by Lamarck as early as 1778: "*One will first remark a large number of bodies composed of raw, dead material which increases by the juxtaposition of the substances forming it and not because of any internal principle of development. These beings are generally called inorganic or mineral beings…Other beings are provided with organs appropriate for different functions and are blessed with a very marked vital principle and the faculty of reproducing their like. They are comprised in the general denomination of organic beings*" [7]. By 1815, Lorenz Oken (1779–1851) used the term "biology" to define the science of life [8]. Oken became a favorite of Goethe whose influence was immense and attracted the young scholar to Jena. In 1802 Oken sketched his own animal classification scheme published in "*Grundriss der Naturphilosophie*" [9]. Here he named the Dermatozoa (invertebrates), Glossozoa (fishes or true tongues), Rhinozoa (lizards, nose and mouth to inhale air), Otozoa (birds, open ear), and Ophthalmozoa (mammals, all organs of sense are complete). Lamarck immediately utilized the word "*and all faculties proper to each of these beings without exception must constitute the unique and vast subject of Biology*…." The entire construct of the term life took a quantum leap in mankind's understanding. The *Grande Encyclopédie* noted that life "is the opposite of death." Now in the eighteenth century, Bichat noted life is "*the sum of the functions that oppose death*." He would take this view and open up our understanding of diseases [10]. Goethe defined life as "*the force that resists laws governing inanimate bodies*." He would go on to investigate comparative anatomy at its very beginnings [11]. Liebig an early chemist called life "*the motor force that neutralizes the chemical forces, cohesion and affinity acting between molecules*" [12]. And Immanuel Kant called it an "*internal principle of action*" [13].

But medicine indeed lagged behind biology and evolution. In a little heralded treatise, Alexander Carolus Curtius wrote in 1662, "*In this world of ours, full of rocks (because our first parents showed a rock-stubborn disregard for the precepts of their Creator), among other discomforts and diseases which are a prelude to that fatal return into dust and ashes, he stone equally infests all- the highest, the middle class and the lowest. No one feels secure from this hail of stones: neither in the air, nor on earth, nor in the sea. Its cloud follows those who go far away and are densely covered by the pilgrims dust; it finds those who dread foreign soil; it comes uninvited to people bent over books and papers. Although it does not spare even those who eat moderately, its particular delight is to torture those who eat their fill. A physician, then, has a good reason to speak of such a universal evil*" [14]. Curtius was a scholarly Lithuanian who came to New Amsterdam to teach classic languages. He returned to Leiden after just 2 years and finished his medical degree. He sought the cause of stone formation in his treatise, "*The more proximate cause that makes the stone matter remain and accumulate in the kidneys or bladder is, above all, the innate or acquired weakness of these organs, in particular to propensity of the kidneys to form sand or stones which Fernelius called the most contributing and most frequent cause of this evil. 'Whoever', he said, 'inherited it from his parents will hardly escape the tortures of the stone'*" [14]. He continues his speculations and dismisses most of the ancient notions of "heat," "narrowness" within the kidneys, and "stupor" and states "*We think, therefore, that this propensity to form stones is some unknown quality*" [14]. His frankness is refreshing from medical philosopher. He falls back on the one thing he derided earlier in his treatise, a sensible diet but falls immediately back to the nostrums of a bygone age: "*Such remedies are: nephritic wood, sponge's, lynx's and Jew's stone, the eyes of crayfish, properly prepared ashes of millipedes, red chickpeas, goat's blood, cubebs, cinnamon, millets, saxifrage, radishes, medlar and apricot seeds, cherry stones and roots, burs, bitter almonds, creeping, betonic and climbing ivy,* *amber oil, juniper oil and many other preparations which can be found in the writings of good authors*" [14].

Evolution of Evolution

The biology of concretions parallels the story of how the theory of evolution came to be such an essential pillar of modern biologic science. Evolution could not have properly conceived without the concurrent establishment by naturalists of the science, taxonomy, comparative anatomy, and biochemistry. No development of a theory of evolution would have been possible without the development of taxonomy or the study of living beings and their relationship to each other. Carl Linnaeus (1707–1778) is considered the father of this science; a physician and botanist, he published his *Systema Naturae* in 1735 [15]. Erasmus Darwin started a Linnaean Society in England and became a serious botanist himself. Linnaeus's literally sent an army of gifted researchers all over the world that sent back specimens for him to classify. Comparative anatomy followed in the wake of specimen collection, with Buffon, Goethe, Pallas, Lamarck, Vicq d'Azyr, and de Jussieu all becoming adept. The second-generation anatomists who went even further included Cuvier (Lamarck's nemesis), Owen (Darwin's nemesis), Charles Robert Darwin, and Huxley (Darwin's bulldog). Finally organic chemistry followed in the wake of Lavoisier, Berzelius, Liebig, Wöhler, and Dumas.

Georges-Louis Leclerc (1707–1788, also Count Buffon) was a French natural philosopher and writer who had massive influence in his own time and profoundly changed the early course of biology [16]. He was from a wealthy family and devoted much of his 81 years of life to the study of the living world. His first love, however, was Newtonian physics, and he was the first to translate Newton's "*Fluxions and Infinite Series*" into French, following in the footsteps of Voltaire who also was a popular translator of Newton: "*Behold, all that which seemed difficult or impenetrable in Newton is here, however, within our grasp*" quipped local opinion [16]. Buffon developed an early interest in Botany, spurred possibly by the Reverend Stephen Hales's "*Vegetable Staticks*" which he also translated into French. His first published text was the introduction of this translation, "*It is through these keen, reasoned, and sustained experiments that Nature is forced to show her secrets: all other methods have never succeeded*" [16]. By 1739, Buffon was profoundly into botany and within 3 months became a member of the French Royal Academy of Science and the superintendent of the King's Garden (Jardin du Roi).

Buffon used his position and royal connections to undertake his life's work, a publishing project that had not been attempted since Pliny the Elder, a complete conceptualization of natural history with his friend and physician, Louis Daubenton [17]. The original 15-volume planned work blossomed into a herculean 44 volumes called "*Natural History, General and Particular.*" "Buffon then appears as the awaited prophet, he comes to fulfill a long-deferred promise: the creation of popular science," stated Lafuente and Saraiva. Buffon became the epitome of eighteenth-century biologic scholarship and began the slow rise of evolutionary theory. He was ultimately literati, capable of weaving a finely crafted tale. In one saga, Buffon's treatment of the "myth of the swan's song" towards the end of his life demonstrates his expressive abilities after having just suffered from renal stone disease himself: "*Moreover, the ancients were not content to make the swan a marvelous singer; alone among all the beings that shudder in the face of destruction, it still sang at the moment of its last agony, and heralded its last sigh with harmonious sounds; it was, they said, when the swan was about to expire and was saying a sad and tender good bye to life that it rendered it strains so sweet and so touching…One heard this song at dawn, when the wind and the waves were calm, and could even see swans musically expiring while singing their funeral hymns. No fiction in natural history, no fable of the Ancients, has been more celebrated, more repeated, given more credit…One must pardon them their fables: they were appealing and touching; they were sweet symbols for sensitive souls. Swans, of course, do not sing when they die; but when speaking of the* *final flight and last burst of great genius about to be extinguished, one will render with emotion that touching expression: "it is the song of the swan"*" [18]. This was from a man who had just nearly died from severe renal colic and whose life was in the final act. Another admirer recalled posthumously (Cubières):

> *One day, I remember, he read me the history*
> *Of the harmonious swan. One saw in his eyes*
> *Shining with the light of creative talent.*
> *But soon his career was to end,*
> *And already the tomb had opened beneath his feet.*
> *Alas! Who could have told me that in that fatal moment*
> *Death was not far, and that swan himself,*
> *The unfortunate approached his final hour!* [18]

Buffon shared his account of stones and his management with his friend and colleague from America, Benjamin Franklin. Franklin had too developed painful bladder stones. He was debilitated and like Buffon had sought counsel of surgeons. Given both their great ages, surgery was ill advised as being too dangerous. Franklin was prescribed laudanum but was frightened of becoming addicted to this drug. Buffon recommended famously to his friend blackberry preserves as a tried and true remedy [19]. Buffon succumbed to another kidney stone attack on April 16, 1788, at the age of 81. He had an autopsy at his own request with supposedly 57 stones accounted for in his urinary tract. Franklin too suffered to his very end from stone disease; often he would have to catheterize himself to dislodge these painful concretions from his bladder outlet. It is a fact that Franklin had patented the first catheter in the USA to help his older brother and ultimately used by himself.

Modern evolution is now much more than a theory; it has become the cornerstone for the whole of biology. The notions of Buffon were passed on to Erasmus Darwin, John Hunter, and Lamarck who each in turn seriously considered it the better hypothesis for their own observations [20]. Lamarck drew such fierce opposition in Paris by his colleague Cuvier that he ultimately died a pauper with his family destitute [21]. Mr. Hunter spent every last cent of his significant fortune following every single anatomical lead on his quest to understand the connections between animals, also leaving his family destitute [22]. Dr. Darwin's comments in turn affected a certain young Dr. Grant back at his own *alma mater* the University of Edinburgh. It was Dr. Grant who took the fledging physician Charles Robert Darwin under his wing for his brief sojourn at medical school [23].

The modern synthesis of biologic evolutionary science awaited the twentieth century but has not stopped evolving itself [24]. Based upon genetics and molecular biology, whole new systems of classification have been developed, and the very notion of life itself is being rewritten. Carl Woese (1928–) is one of those gargantuan paradigm-shifting scientists whose work was dismissed for many years but has literally transformed biology. He was a microbiologist and physicist who defined the new kingdom of life called Archaea in 1977 [25]. Woese pioneered the use of ribosomal RNA (16S) to redefine biological relationships that were originated by Carolus Linnaeus [26]. He literally redrew the taxonomic tree into a three-domain system which has 23 main subdivisions. Most of these lineages are single-celled organisms that make up the bulk of the Earth's biomass. Many of these organisms live upon and within the rocks and stones beneath the earth's surface [25]. It is apropos that perhaps much of the life forms on our planets are chemolithotrophs that literally metabolize stones, while the remaining organisms can suffer from calcareous concretions that pathologically effect their organs. Professor Norman Pace has said of Woese, "*I think Woese has done more for biology writ large than any biologist in history, including Darwin*…." [27].

Biologic Concretions: Plants

One might think that plants might have a lengthy history of speculative investigation about health and disease, but sadly the ability to investigate the anatomy and physiology of these sedimentary living organisms required much more sophisticated apparatus. A phytolith comes from the Greek roots "plant stone." The first printed literature came from a German botanist G.A. Struve in 1835. Struve came from a family producing generations of scientific scholars (similar in fact to the Darwin clan), one of which happened to be a geologist (Heinrich Christian Gottfried von Struve) whose name would grace the mineralogical nomenclature with a common component of stones, struvite (magnesium ammonium phosphate hexahydrate). About 1 year following this fateful observation, another botanist, Christian Gottfried Ehrenberg began to analyze plant samples from his friend and explorer, Charles Darwin following his tour aboard the *HMS Beagle* [28].

Most phytoliths are derived from root absorption of the soluble monosilicic acid and laid down as silicon dioxide. The function(s) of phytoliths in plants is debated, but plants grown in silicon-free environments do not grow as well. The phytolith is thought to act as a free-radical scavenger, protecting the plants from ultraviolet radiation [28]. Calcium oxalate phytoliths get a special name, raphides, and probably evolved added specialized functions in metabolism [28]. They serve as a reservoir for carbon dioxide and may help in the preservation of water, as well as retarding the burning potential of the plant since flammability is always a risk to immobile plants.

Calcium oxalate in plants was investigated by an early Linnaean convert, Dr. Robert Brown. He too developed a passion for botany in medical school in Edinburgh. He dropped out of school and entered the Royal Navy as a surgeon. He traveled extensively in Ireland and developed a reputation as first rate observer and came to the attention of Sir Joseph Banks. He became the ship's surgeon (HMS Investigator) and head naturalists on a mission to Australia (then New South Wales) and brought back copious specimens of plants and animals [29]. Of the 3,800 botanical specimens, about 120 of them were orchids, a favorite of Charles Darwin. He was invited to become the chief librarian and researcher for Sir Joseph Banks and also became the president of the Linnaean Society. In this capacity, he interacted with many of the notable researchers of his era. He even took time from his precious microscopic studies to demonstrate the intracellular streaming of protoplasm to a young naturalist just back from his famous voyage, Charles Robert Darwin. He had just won the Copley Medal from the Royal Society. He is famous today for naming the cell's nucleus, describing Brownian motion, immortalized by Albert Einstein. In one final interweaving bit of trivia, his death from "dropsy" (edema) on June 10, 1858, left open a serendipitous slot for someone to present a paper. The June meeting was cancelled in honor of Brown, a new vice president was needed, and a meeting was called for July 1, 1858, and J.D. Hooker's withdrawal of his paper paved the way for both Charles Darwin and Alfred Russel Wallace papers to be presented that evening on natural selection [24].

Biologic Concretions: Animals

Human stone disease has been known since the foundations of recorded history, but the occurrence in animals has also been apparent. Dogs were perhaps the first domesticated animal with all modern breeds arising from the common root stock, the Gray wolf at least 25,000 years ago. These animals form stones in the wild, and at least 26 breeds of domesticated dogs likewise make stones and suffer as humans do. Cats also were domesticated and used by the ancient Egyptians, and they also are stone formers. Most domesticated ruminants form stones; the horse forms stones, the goat, and sheep. In the wild, the actual stone-forming activity is much less known, but probably occurs. Swine form stones, as do lagomorphs (rabbits). The actual diversity of stone formation in animals is literally underappreciated. In many mammals, fish, birds, reptiles, amphibians, and insects all have urinary tracts and have some risk of stone formation. The mitochondrion (originally called a "bioblast" by Richard Altmann in 1894 but renamed by Carl Benda in 1898) which is the organelle that generates the energy for the functioning of a cell's activities itself has concretions, called simply "*granules*" [30]. The function of these granules is not entirely clear, though they seem to perform as a sink for cations (positively charged ions), especially calcium [31]. The mitochondrion of eukaryotic cells themselves are more likely "*symbiotes*" that have adapted to the cellular existence from a prokaryotic progenitor similar to that of Proteobacteria and closely related to the rickettsia. This endosymbiotic relationship was popularized by Lynn Margulis [32].

A wide variety of animals form urinary stones, and most of them follow pathways that similarly effect humans. In fact, the variety of animal stone types closely parallels those of humans with some minor variation which would surprise no mineralogist. One recent review article noted stones in 27 varieties of animals from oysters to whales [33]. In a more extensive search, several microorganisms, many insects, and other invertebrates all form concretions; much of the problem in these realms is that the literature is broad, and scientific writings are dense reading, limiting access to knowledge by another specialist. Consider the kissing bug, for instance. This is *Rhodnius prolixus*; it consumes a diet that is protein rich, the blood of other animals. Its metabolism has adapted to the large amounts of nitrogenous wastes by excreting uric acid via its lower Malpighian tubules [34]. *Rhodnius* is the vector for trypanosomal infections to humans. It has been hypothesized that Charles Darwin was infected with Chagas' disease by this particular stone-forming insect [35].

Yet with a little effort, this list can be rapidly expanded (Table 11.1). In fact, the list of stone-forming animals can be categorized utilizing any of a number of ancient methods; however, it becomes apparent that many groups of animals can form concretions within their assundried urinary tracts. Since this is a chapter on evolution, let's look at a peculiar group of animals that most represents this stone disease phenomenon. These groups of animals are terrestrial mammals that have returned to the water or sea. This group includes a diverse series: the elephants, carnivores (includes a whole host of families from bears to cats), and ruminants (a whole broad group from horses to pigs). The elephants that returned to the water became the manatees, the sirenians. There are three remaining groups of these animals, the Amazonian manatee, the dugong, and the West Indian manatee. Elephants themselves are prone to calcium oxalate and struvite stones [36]. That manatees likewise have been reported with struvite stone disease therefore should not come as a surprise [37]. A bearlike animal returned to the water 23 million years ago, and one of the earliest known ancestors is *Puijila darwini* [38]. The bears that returned to the sea became the pinnipeds or seals, and there are currently three families that all form stones. The elephant seal is the largest stone-forming pinniped. The California sea lion is an ear seal or Otariidae that not only forms stones as well as performs in circuses [39]. The ruminants that returned to the water became the whales (cetaceans which include dolphins and porpoises as well) and probably later to become the hippopotamus. Ungulates are the herbivorous mammals that routinely form stones, so it would be no great surprise if carnivorous ungulates that returned to the oceans would take their stone-forming tendencies with them to suffer in an aquatic realm [40]. The sperm whale, the bottle-nosed dolphin, and the porpoise have all had reported uric acid and calcium phosphate stones [41]. Finally there are weasels that are returning to the sea as the otter. Some bears also are highly aquatic, such as the polar bear. All of these mammals are stone formers.

Darwin's Dilemma

The year 2009 marked the bicentennial of Charles Robert Darwin's (1809–1882) birth and the sesquicentennial of the publication *On the Origin of Species by Means of Natural Selection, or the Preservation of Favored Races in the Struggle for Life* [42]. Darwin clearly expressed his admiration of his grandfather Erasmus in his own autobiographical sketch and by naming his first transmutation notebook "*Zoonomia*" [43]. Both Charles and Erasmus were remarkably gifted intellectuals and both were highly innovative theorists. Each Darwin managed to leave numerous epistemological dilemmas in their wake [44]. The forgotten third Darwin is Charles, son of Erasmus and uncle to Charles Robert of evolution fame, and he will be our final connection to the history of stone disease.

It is also the 220th anniversary of the publication of "*The Botanic Garden*" from Charles Darwin's grandfather, the physician polymath, Erasmus. Erasmus climbed into popular culture with this lengthy poem that delved into the scientific intricacies of the sexual lives of plants. Both Darwins were strong proponents of the importance of sexuality in theory and practice. Erasmus had 12 legitimate and

Table 11.1 Animals with known inorganic or organic concretions (**bold** are classes with stone disease, and *italics* are for species with stone disease)

Phylum (currently 29 listed phyla by LPSN, 32–39 are also typically listed)	Species
1. Choanoflagellata	140 species of single-celled
2. Porifera (sponges)	~5,000 species
3. Placozoa	*Trichoplax adhaerens* (only one)
4. Cnidaria (jellyfish, sea anemones, corals, starfish)	10,000 species
Coelenterata	*Renilla reniformis*
	Aurelia aurita
5. Ctenophora (comb jellies)	~80 species
6. Sipuncula	150 species
7. Mollusca	50–150,000 species
Gastrapoda	*Ferrisia wautieri*
	Helix pomatia
Lamellibranchia	*Mercenaria mercenaria*
8. Annelida	15,000 species
9. Onychophora (velvet worms)	110 species
10. Arthropoda	~3.7 million species
Trilobitomorpha	
Chelicerata (spiders, mites, scorpions, horseshoe crab)	
Crustacea [shrimps, barnacles (studied intensely by Charles Darwin), lobsters, crabs]	
Onychophora	
Diplopoda	
Hexapoda (Insecta and Entognatha)	
11. Bryozoa	5,000 species
12. Entoprocta	150 species
13. Platyhelminthes (the flatworms)	
Turbellaria (aquatic)	4,500 species
Trematoda (flukes, 1,500 species)	*Cyanthocotyle bushiensis*
Cestoda (tapeworms, 3,400 species)	*Taenia taeniaeformis*
Monogenea (ectoparasites, 1,100 species)	
14. Nemertea (ribbon worms)	1,400 species
15. Rotifera (rotifers)	2,200 species
16. Cycliophora	3 species
17. Gastrotricha	700 species
18. Gnathostomulida (jaw worms)	100 species
19. Chaetognatha (arrow worms)	120 species
20. Nematoda (round worms)	80,000 species
21. Nematomorpha	350 species
22. Priapulida	18 species
23. Kinorhyncha	150 species
24. Loricifera	~100 species
25. Xenoturbellida	2 species
26. Acoelomorpha	
27. Phoronida	12 species
28. Brachiopoda (lampshells, molluscs)	12,000 species
29. Echinodermata (sea lilies, starfish, sea urchins, sand dollars, sea cucumbers, brittle stars)	17,000 species

(continued)

Table 11.1 (continued)

Phylum (currently 29 listed phyla by LPSN, 32–39 are also typically listed)	Species
30. Hemichordata (acorn worms)	70 species
31. Chordata (vertebrates)	~100,000
Urochordata (tunicates)	
Cephalochordata (lancelates)	
Vertebrata	60,000 species
Mammalia	
• **Subclass** Prototheria: monotremes—echidnas and the platypus	
• **Subclass Theriiformes**: live-bearing mammals + prehistoric relatives (†)	
º Infraclass †Allotheria: multituberculates	
º Infraclass †Triconodonta: triconodonts	
º Infraclass Holotheria: modern live-bearing mammals and their prehistoric relatives	
▪ Supercohort Theria: live-bearing mammals	
▪ Cohort Marsupialia: marsupials	
▪ Magnorder Australidelphia: Australian marsupials and the monito del monte	
▪ Magnorder Ameridelphia: New World marsupials	
▪ Cohort Placentalia: placentals	
▪ Magnorder Xenarthra: xenarthrans	
▪ Magnorder Epitheria: epitheres	
▪ Grandorder Anagalida: **lagomorphs, rodents**, and elephant shrews	
▪ Grandorder Ferae: **carnivorans, pangolins,** †creodonts, and relatives	
▪ Grandorder Lipotyphla: **insectivorans**	
▪ Grandorder Archonta: bats, **primates,** colugos, and tree shrews	
▪ Grandorder Ungulata: **ungulates**	
▪ Order Tubulidentata *incertae sedis*: aardvark	
▪ Mirorder Eparctocyona: †condylarths, **whales, and artiodactyls (even-toed ungulates)**	
▪ Mirorder †Meridiungulata: **South American ungulates**	
▪ Mirorder Altungulata: perissodactyls (odd-toed ungulates), **elephants, manatees, and hyraxes**	

Protozoa *Proroden morgana*

2 illegitimate children, and Charles fathered 10 children with his wife Emma in their first 17 years of marriage. Charles printed his ideas on the importance of sexual activity in "The Descent of Man, and Selection in Relation to Sex." Their combined opinions on sexuality certainly caused a significant dilemma during the Victorian era [44].

Charles became a gifted naturalist during his circumnavigation voyage on the *HMS Beagle* and at age 28 began his speculation on evolution. He became a prolific collector and writer, returning with a 770 page diary, 1,383 pages of geology notes, 368 pages on zoology, 1,529 creatures in spirits, 3,709 stuffed birds, animal skins, and one half eaten "Petise" [43]. Erasmus was a physician, polymath, and author who was a dedicated naturalist and botanical icon. Erasmus drew the ire of English intellectual scientists and clergy, but Charles took on the world's. Both Darwins were not shy in their use of anthropomorphisms in describing their love of natural things, life, which sadly in modern biologic research is no longer acceptable [44]. Erasmus did contribute a piece on stone disease and opened up a pathway for early protochemists to investigate the physiology of the kidneys.

Zoonomia

Erasmus Darwin (1731–1802) was widely regarded in his own time as a great poet, natural philosopher, and writer. He spent his life in the Midlands of England as a very busy horse-and-buggy doctor [45]. His poetry made him famous though he did contribute to the English scientific mainstream via the Royal Society. He was a founder of an influential group of natural philosophers called the Lunar Society of Birmingham. His most highly influential scientific work was called *Zoonomia* (1794–1796), and it is mostly medical and biologic [46]. He showcases his intellectual uniqueness, but he was known to have borrowed significantly from the ideas of another polymath, Dr. David Hartley.

We've already met David Hartley (1705–1757) as the champion to Mrs. Stephens' secret nostrum. He was intent on following his father's footsteps to become an Anglican minister, but his questioning mind did not allow him to take the "orders" because he disagreed with the 39 Articles at Cambridge. He took up medicine instead as well as natural philosophy, experimental physiology, and writing. His main significant writing was "*Observations on Man, his Frame, his Duty, and his Expectations*" published in 1749 [47]. He was elected as a member of the Royal Society in 1736 and began to investigate the methods of stone dissolution, perhaps prompted by his own sufferings from bladder stones. He tried to incorporate the laws of Newton to the actions of man. He was interested in the works of Locke and Condillac and the notion of the physical nature of leaning, knowledge, memory, and voluntary actions. He was highly thought of and attracted the attentions of Joseph Priestley (1733–1804), a member of the Lunar Society [48]. It is via these webs of connections that his work probably influenced Erasmus Darwin.

Dr. Darwin also anticipated the great debate regarding the mutability of species: "*Would it be too bold to imagine, that in the great length of time, since the earth began to exist, perhaps millions of ages before the commencement of the history of mankind, would it be too bold to imagine, that all warm-blooded animals have arisen from one living filament, which THE GREAT FIRST CAUSE endued with animality, with the power of acquiring new parts, attended with new propensities, directed by irritations, sensations, volitions, and associations; and thus possessing the faculty of continuing to improve by its own inherent activity, and of delivering down those improvements by generation to its posterity, world without end!*" [49].

Zoonomia; or the Laws of Organic Life was a two-volume work that was brought out in sequence, the first in 1749 and volume II 2 years later. Zoonomia was Dr. Darwin's attempt to apply Linnaeus's taxonomy to the knowledge of animals and link this to disease and medicine. From this standpoint, he simply accomplished in his own enigmatic way to develop a medical nosology which his professor of medicine at Edinburgh was developing as well. In volume I, Darwin establishes a rather unique basis of disease classification into four parts. In fact, one of his most quoted passages has also to do with evolution and still includes his hierarchical classification. Here there are "diseases of irritation" that arise from external causes. Next he specifies "diseases of sensation" which arise from such factors as excess pain or pleasure. Next are "diseases of volition" which are caused by desire or aversion. The fourth class includes the "diseases of association" which are caused when diseases of one organ system cause other associated problems. In his chapter entitled "*Of Generation*," he famously quips, "*…the Great First Cause endowed with animality, with the power of acquiring new parts, attended with new propensities, directed by irritations, sensations, volitions and associations: and thus possessing the faculty of continuing to improve by its own inherent activity, and delivering down those improvements, by generation and posterity, world without end!*" [49].

Let us specifically look at what Dr. Erasmus Darwin thinks about urolithiasis. In volume II beginning on page 23, he comes to section 9 which he calls "*Stones of the kidnies and bladder*." Since he is taxonomizing, his name for this disease is *Calculus renis* or stone of the kidney. He differentiates the presenting symptoms of flank pain prior to moving to theory of formation of stones: "*Where the absorption of the thinner parts of the secretion takes place too hastily in the kidneys, the hardened mucus, and consequent calculous concretions, sometimes totally stop up the tubuli uriniferi; and no urine is secreted. Of this many die, who have drunk vinous spirit, and some of them recover by voiding a quantity of white mucus, like chalk and water; and others by voiding a great quantity of sand, or small* *calculi*" [49]. He supposes that stones, thus formed in the kidneys, become the nidus of bladder stones: "*This hardened mucus frequently becomes the nucleus of a stone in the bladder*" [49]. He then differentiates stones from gravel, "*The salts of the urine, called microcosmic salt, are often mistaken for gravel, but are distinguishable both by their angles of crystallization, their adhesion to the sides or bottom of the pot, and by their not being formed till the urine cools. Whereas the particles of gravel are generally without angles, and always drop to the bottom of the vessel, immediately as the water is voided*" [49]. He then begins to speculate on both the proximate and remote causes of stone formation: "*Though the proximate cause of the formation of the calculous concretions of the kidneys, and of chalk-stones in the gout, and of the insoluble concretions of coagulable lymph, which are found on membranes, …consists in the too great action of the absorbent vessels of those parts; yet the remote cause in these cases is probably owing to the inflammation of the membranes; which at the time are believed to secrete a material more liable to coagulate or concrete, than they would otherwise produce by increased action alone without the production of new vessels, which constitutes inflammation*" [49].

As an acute observer of nature, he continues by comparing stone formation to the formation of other complex animal structures such as hair, silk, scales, horns, and fingernails. He compares the similarity of gallstone formation. He discusses the similarity to forming the healing callus from a bone fracture and the inflammation in the periosteum. Finally he ends this section with comparison to shell formation of animals like snails, the eggs of birds, and "the annually renewed shells of crabs." He moves on to current chemistry knowledge, stating "*All these concretions contain phosphoric acid, mucus, and calcareous earth in different proportions; and are probably so far analogous in respect to their component parts as well as their mode of formation. Some calcareous earth has been discovered after putrefaction in the coagulable lymph of animals. Fordyce's Elements of Practice. A little calcareous earth was detected by Scheel [Scheele] or Bergman in the calculus of the bladder with much phosphoric acid, and a great quantity of phosphoric acid is shewn to exist in oyster-shells by their becoming luminous on exposing them a while to the sun's light after calcination*" [49].

As only Erasmus could, he concludes his section of urolithiasis with a proposed treatment for stone disease: "*Now as the hard lumps of calcareous matter, termed crabs' eyes, which are found in the stomachs of those animals previous to the annual renewal of their shells, are redissolved, probably by their gastric acid, and again deposited for that purpose; may it not be concluded, that the stone of the bladder might be dissolved by the gastric juice of fish of prey, as of crabs, or pike; or of voracious young birds, as young rooks or hawks, or even of calves? Could not these experiments be tried by collecting the gastric juice by putting bits of sponge down the throats of young crows, and retracting them by a string in the manner of Spallanzani? or putting pieces of calculus down the throat of a living crow, or pike, and observing if they become digested? and lastly could not gastric juice, if it should appear to be a solvent, be injected and born in the bladder without injury by means of catheters of elastic resin, or caoutchouc?*" [49].

Charles Darwin: The Uncle

Charles Darwin (1758–1778) was the eldest son of Erasmus Darwin and his first wife Mary Howard. From all accounts, he was an exceedingly gifted young man with broad scientific aspirations [50]. He began his academic career at Oxford and Christ Church College in 1774, but he lacked his father's classical talents. He entered into the medical school at the University of Edinburgh in late 1775 or early 1776. He immediately came to the attention of a rising junior faculty member Andrew Duncan who became his mentor as well as his landlord. Charles communicated frequently with his father about his growing interests in medicine and physiology. His life was tragically cut short by inoculating himself with meningococcal meningitis after performing an autopsy [50]. Charles was most certainly influenced by Robert Whytt's legacy (1747–1766), his successor William Cullen, and his successor James Gregory who was Darwin's professor of medicine. For his medical studies up until March of 1778, Charles had received the gold medal for his dissertation.

Charles showed no inclination or interest in urolithiasis, sadly. However, of his three surviving investigative writings, one certainly leaps out to the student of stone lore. It is Charles Darwin's medical thesis entitled "*Experiments establishing a criterion between mucaginous and purulent matter. And an account of the retrograde motions of the absorbent vessels of animal bodies in some diseases*" [51]. His father, Erasmus had this work published posthumously from Lichfield in 1780, and Charles speculates that another pathway might exist bringing sugar (glucose) to the kidneys of patients with diabetes mellitus. Two future founding fathers of stone science would both comment upon the tragic young doctor's hypothesis and perform detailed investigations upon Darwin's mysterious or invisible pathway. These were William Hyde Wollaston and Alexander Marcet.

William Hyde Wollaston was born in Norfolk in 1737 and attended Gonville and Caius College, Cambridge, in 1793. He developed a practice in medicine but soon focused his considerable energies to chemistry, crystallography, metallurgy, and physics. He was elected a fellow of the Royal Society in 1793 and developed a secret process of processing platinum which made him a fortune. He also discovered the elements palladium and rhodium. He was much interested in the chemistry of stones. In 1811, Wollaston published a paper that supported the observations of the young Edinburgh medical student, Charles Darwin. His paper was entitled "On the non-existence of sugar in the blood of persons laboring under diabetes mellitus." In this fascinating early work on serum chemistry, Wollaston follows the pathways of two metabolites, oxalic acid and sugar, in the serum of patients. He develops an ingenious experiment that was employed upon volunteers who were sampled at intervals following ingestion of a trace substance. He states "*In order to account for the presence of sugar in the urine, we must consequently either suppose a power in the kidneys of forming this new product by secretion, which does not seem to accord with the proper office of that organ; or, if we suppose the sugar to be formed in the stomach by a process of imperfect assimilation, we must then admit the existence of some channel of conveyance from the stomach to the bladder, without passing through the general system of blood-vessels. That some such channels does exist, Dr. Darwin endeavored to ascertain, by giving large doses of nitre, which he could perceive to pass with the urine, but could not detect in its passage through the blood; and he imagined the channel by which it was conveyed to be the absorbent system, upon the supposition that they might admit of a retrograde motion of their contents*" [52]. Wollaston looked for traces of his prussiate in saliva, exudates of blisters, the serum, and in urine. He speculates that there might be as yet unknown mechanism of transfer of substances to the kidneys and the production of urine. In the follow-up to this paper, his colleague and pupil Alexander Marcet also presents his own experiments on patients at Guy's Hospital [53]. He too cannot find these substances in the blood but also question the methods. He notes he shared his data with two fellow investigators, Dr. Henry of Manchester and Dr. R. Pearson of London who would also go on to become a founding father of stone chemistry. None could yet explain these most vexing observations of the now dead Charles Darwin.

The Muse and the Malady

Erasmus Darwin's restless mind was not content with his botanical garden [54]. His quite but busy medical practice allowed him to develop a like-minded group of natural philosophers that surrounded him in the remarkable English Midlands. Sometime between 1757 and 1758, Erasmus Darwin and Matthew Boulton the industrialist who lived at nearby Birmingham decided to form a dinner group to discuss and promote enlightenment ideals. There were 14 known members over the years including the following: Matthew Boulton, Erasmus Darwin, Thomas Day, Richard Lovell Edgeworth, Samuel Galton, Jr., James Keir, Joseph Priestley, William Small, Jonathan Stokes, James Watt, Josiah Wedgwood, John Whitehurst, and William Withering. This group would meet informally on evenings of full moons therefore earning the nickname of members called Lunaticks [55].

Dr. Darwin had a particular affinity to the work and writings of one particular Lunatick, Joseph Priestley [56]. Priestley (1733–1804) was a liberal-minded theologian and dissenting English minister. He also was brilliant at chemical research and developed the notion of phlogiston [57]. After his arrival in Leeds, his natural philosophizing increased dramatically. He presented five papers to the Royal Society between 1767 and 1770. He considered traveling with Captain James Cook on his voyage to the South Seas but this was not to be. He did develop a method of providing the sailors with soda water, which he believed might cure scurvy. In 1772 he published his *Directions for Impregnating Water with Fixed Air* which following in the steps of his mentor Benjamin Franklin he would not patent [58]. The carbonated water was thought to have significant medicinal effects and was widely touted in treating with patients suffering from stone disease. Others, in particular J.J. Schweppe from Switzerland, would patent the idea and make their family fortunes. Schweppe developed one specific type of "fortified water" for treating stone patients [59]. In 1773, Priestley won the Copley Medal of the Royal Society for his distinguished contributions.

In Edinburgh, Joseph Black (1728–1799) published his famous dissertation *De humore acido a cibis orto et magnesia alba* (Experiments Upon Magnesia Alba, Quicklime, and Some Other Alkaline Substances) [60]. Black was fully aware of Whytt's famous earlier experiments on the use of limewater to try to dissolve the stones of stone sufferers. In fact, Whytt was currently contending with his colleague Charles Alston, another professor at Edinburgh, as to the best source of quicklime, cockleshells or limestone. Whytt championed the notion that quicklime when first removed from the fire was the most powerful solvent for stones. Black stepped into this debate early in his medical school career. He began examining absorbent earths to discover a more powerful lithotriptic. By avoiding the investigation of limewater, he sidestepped his two professor's differences. He chose the white powder magnesia alba, used at the time as a purgative and first described by the German chemist Friedrich Hoffman [61]. He heated the magnesia alba and noted that there were unexpected properties; that is, it gave off a gas, "fixed air" that extinguished an adjacent candle. His work attracted the attentions of others including Mac Bride, Cavendish, Priestley, and Rutherford. His colleague and Whytt's successor William Cullen encouraged the studies of Black. Black would publish nothing further in these researches, but he corresponded widely with others, Priestley in particular, and became the student's favorite teacher. His favorite dinner club was the Oyster where he often dined with his two best friends, Adam Smith and Dr. James Hutton. Black was called in to attend the tragic death of Charles Darwin.

Conclusions

J. Swift Joly became interested in stone disease at St. Peter's Hospital for Stone Disease in London. He wrote, spoke, and operated and did research on urolithiasis. In one particular address on The Formation of Urinary Calculi presented to the Royal Society of Medicine on February 23, 1928, he spoke specifically about the evolution of kidneys and the development of urolithiasis [62]. He deserves quoting at some length, so we will present his whole paragraph:

> "*Here it may be interesting to cast a glance at the functioning of the kidneys of the lower animals. As far as we know, mollusks and crustacean eliminate most of their nitrogenous waste as uric acid or guanin. Uric acid forms the greater part of the excreta of insects. In fishes and amphibian its place is taken by urea. These animals obviously never had any need to conserve water, and their urine is exceedingly dilute. The only chemical examination of fish urine I know of, gave a urea concentration of less than one part in a thousand, while frogs excrete their own volume of urine every day.*

When we come to the reptiles, and their descendents, birds, we find that they have reverted to the primitive type of excretion, and eliminate their nitrogenous waste in the form of uric acid, or more strictly speaking, urates. Reptiles first appeared in the Permian era- at least these are the earliest rocks in which their remains have been found. The Permian immediately followed the Carboniferous era. Geological evidence indicates that in the lower Carboniferous era, the land was low and marshy, and that large tracts were under shallow seas. These conditions favored amphibian life, and in the rocks of this era the remains of the first amphibians were found. The later part of the Carboniferous and the whole of the Permian ages were times of 'emergence and mountain-building.' The earliest terrestrial animals, primitive reptiles appeared in this era, and their remains have been found in the rocks belonging to it. The amphibian of the lower Carboniferous times were stranded high and dry by the elevation of the land, and had to adapt themselves to dry and arid conditions in order to survive. It was, therefore, most important for them to conserve water. One of the means adopted was to secrete solid urine. Birds and reptiles excrete watery urine from their kidneys, but the water is all absorbed in the cloaca and the lower end of the bowel. If they continued to excrete their waste nitrogen in the form of urea, it would be impossible for them to eliminate solid urine. Urea is exceedingly soluble, and as its solution become concentrated, the osmotic pressure rises enormously. The epithelium of the cloaca and lower bowel would be unable to concentrate the urine to dryness, against this pressure. By returning to the primitive form of excretion, and eliminating their nitrogen as uric acid, they overcame this difficulty. Uric acid is very insoluble, and when the urine became concentrated, it was thrown out of solution, and therefore could not exert any osmotic pressure, so that the animal was able to concentrate the urine to dryness." This is pretty heavy stuff for the evolution of uric acid stones.

Perhaps the greatest dilemma both the grandfather, Erasmus, and modern scientific icon, Charles, embraced was eliminating the role of god in the natural world. Erasmus most certainly formulated a rather distinct impression on the origins of life and species and was considered a Lamarckian. Dr. Darwin designed his own family crest that heralded his ideas on life from life. He emblazoned his coach with this symbol until the Church mandated its removal, *Ex conchia omnia* (all things from shells, Fig. 11.1). Charles eliminated creation from his theory of evolution, making a purely mechanistic biology that could be studied, measured, quantified, and experimented upon, like Newton. The continuing dilemma imposed by these Darwins is best shown by Gallup polls in 1982, 1999, and 2004. 44–47 % of Americans believe that God created human beings and between 37 and 40 % believe that God "guided" evolution (theist); both opinions are diametrically opposed to Darwin's view [63]. It is fascinating that the father of eugenics and cousin to Charles Robert Darwin was Sir Francis Galton, son of Erasmus's daughter Frances Ann Violetta Darwin, from his second marriage to Elizabeth Pole. Pierre Simon Laplace once responded famously to Napoleon regarding his failure to mention "the author of the universe" in his "*Celestial Mechanics*." "*Sire*," Laplace stated, "*I had no need of that hypothesis*." Similarly, Darwin wrote in a letter in 1859, "*I would give absolutely nothing for the theory of Natural Selection if it requires miraculous additions at any one stage of descent*" [64].

Fig. 11.1 Ex conchis Omnia (everything from shells) the motto of Erasmus Darwin, M.D. with crest. This had to be removed from his carriage by clerical authorities

This chapter wanders the byways of the history of biology and medicine on the tenuous trail of evolution, dropping into those aspects that touched on urolithiasis either serendipitously but rarely directly. In the final analysis, our classic model of evolution and the understanding of the genetic basis are analogous to crystal growth, development, and reproduction—all portions of stone generation. This analogy is itself historical with some of the sentinel minds of evolutionary theory using it like Buffon. The Nobel Prize-winning geneticist Francois Jacob concludes his 1973 masterpiece "*The Logic of Life*" with the following: "*In many ways the properties of these structures [*cells*] recall those of crystals. This is an old analogy, already invoked more than two centuries ago to explain the shape, growth and reproduction of organized beings*" [65]. He goes on to elaborate, "*From this point on, the analogy between crystals and living structures regains an operational value. What gives a collection of objects the property of assembling is their sameness. Not only can they form geometrical structures; they can do so spontaneously. But there is no telling how far the sameness must go and what difference in structure can be tolerated. Although constraints on the formulation of three-dimensional crystals appear to be strict, they seem less stringent in other cases, so that nucleic-acid or protein subunits are sufficiently similar objects to be placed in geometrical arrangements*" [65]. It is apt that a metaphor of the building blocks of stone disease has been utilized by a master of evolutionary biology to summarize his very own science! "*Without this property [*life, emergence*] the universe would be insipid: an ocean of identical particles, both inert and unaware of each other; something like the oldest rocks on earth, whose molecules and relationships have not changed for thousands of millions of years*" [65].

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Founding Fathers of Stone Chemistry

12

Introduction

The chemical composition of calculi parallels the infancy of clinical chemistry. One requisite of early chemists was the requirement of an abundant substrate. Calculus disease during the late eighteenth and early nineteenth century was endemic and concurrent with the Industrial Revolution. Thus, stones, particularly bladder calculi, were readily available secondary to the rise in incidence of this disease in England, France, the Netherlands, and Germany. The promise of the enlightened minds did fall short, except for surgery without anesthesia in delivering from the sufferers of stone disease any significant improvement of their condition. In the words of Thomas Jefferson, "*Harvey's discovery of the circulation of the blood was a beautiful addition to our knowledge of the animal economy, but on a review of the practice of medicine before and since that epoch, I do not see any great amelioration which has been derived from that discovery*" [1]. The protochemists were to hand their legacy to real chemists, and the lot of the stone patient was going to dramatically improve. The beginning would require science to pierce the nuances and complexities of biologic fluid chemistry and then solid organic chemistry which required a ready source of material to study. The increased incidence and success removing bladder stones would solve both problems. Now medicine required only the inquiring minds to get to the chemistry of the actual stones themselves. Scheele and Marggraf were touchstones on the pathway to elucidation; now it was time to get to the real chemistry of stone disease.

The New Dawn

The chemical composition of calculi parallels the infancy of clinical chemistry. One requisite of early chemists was the requirement of an abundant substrate. Calculus disease during the late eighteenth and early nineteenth century was endemic and concurrent with the Industrial Revolution. Thus, stones, particularly bladder calculi, were readily available and became the chemical interest of Stephen Hales (Fig. 12.1c). The Honorable Robert Boyle was beginning to write about chemistry in London, while Joseph Black was beginning to teach chemistry at the medical school in Edinburgh [2]. William Cullen thought that chemistry could be applied clinically to sick patients, and the urine was a readily available fluid upon which to study constituents. Cullen (1710–1790) was the leading teaching physician of his day and he influenced many medical students (Fig. 12.1c) [3]. Jöns Jacob Berzelius (1779–1848) had published a treatise on the complexity of urine from Sweden, and the whole field of chemistry became focused upon the urine and stone disease (Fig. 12.1b) [4]. He famously visited London and spent time with Wollaston and Marcet. One student of Cullen's was John Bostock from Liverpool (Fig. 12.1c). He was tutored by

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Fig. 12.1 The founding fathers—segregated. (**a**) French (1) Antoine Lavoisier, (2) Felix Vicq D'Azyr, (3) Antoine Fourcroy, (4) Nicholas Louis Vauquelin, (5) Francois Magendie, (6) Pierre F.O. Rayer, (7) J.B. Dumas, (**b**) European (1) Karl Wilhelm Scheele, (2) Jons Jacob Berzelius, (3) Justus Liebig, (**c**) English (1) Reverend Stephen Hales, (2) William Cullen, (3) Joseph Black, (4) Joseph Priestley, (5) William Hyde Wollaston, (6) Alexander Marcet, (7) John Bostock, (8) William Prout, (9) Richard Bright, (10) Henry Bence Jones, (11) George Owen Rees, (12) Golding Bird

Joseph Black and graduated medicine with a thesis *On Secretions* in 1798 that essentially was on the chemistry of biliary secretions (Fig. 12.1c). He went back to Liverpool to work with Matthew Dobson but moved to London in 1817 and began to teach medical chemistry at Guy's Hospital [5]. In London he pursued his interests in chemistry and gave up the practice of medicine. He became a member of the Royal Society and interacted with another London physician, William V. Cruickshank who was also interested in urine chemistry. Both published papers on the subject [6]. Two other physicians, William Wells (1757–1817) and John Blackall (1771–1860), also noted abnormalities of sick patient's urines but had no interest in urolithiasis, though Wells was interested in a vast number of topics including evolution long before Charles Darwin [7].

In 1776, Karl Wilhelm Scheele (1742–1786) in seminal studies on bladder stones noted that though barely soluble in water, they turned litmus paper red and thus were acidic (Fig. 12.1b). Upon heating, the stones produced an odor of prussic acid. He gave the name lithic acid to the substance and thought that all urinary stones were of similar chemistry. Another chemist T.B. Bergman (1734–1794) made similar observations. George Pearson was a physician/scientist who also attended Edinburgh where he took his medical degree in 1771. He moved to London and obtained a position at St. Thomas's Hospital where he encountered William J. Wells and John Bostock. He became a lecturer at St. George's Hospital and was elected the chief physician on February 23, 1787, which he held for 40 years. In 1795 George Pearson (1751–1828) influenced by both Cullen and Black presented an investigation of 300 stones from the collection of Mr. Heaviside. With exquisite attention to detail, he concluded that lithic acid is not present in the stone but was an oxide. Pearson suggested in his paper to change the name to uric acid, in agreement with Fourcroy who coined the term. Pearson further pointed out that most stones do contain uric acid (194/200) but in varying concentrations. Pearson was elected a fellow of the Royal Society on June 23, 1791, and gave the Bakerian Lecture in 1827. Davies Gilbert best describes Pearson as follows: "*Dr. Pearson was acknowledged by good judges, to be a sound Greek and Latin scholar. He was a hospitable landlord, a disinterested friend, and very good-humoured and jocose companion; he abounded anecdotes, which he took with excellent effect. He would often observe to his friends, that he knew he was growing old; but that he had made up his mind to die 'in harness'*" [8]. Pearson would eventually cross swords with another physician-chemist about some chemical findings. He also influenced the next generation of physician-chemists like Henry Bence Jones.

Antoine-Laurent Lavoisier (1743–1794) became interested in chemistry but never did any significant work on human fluids (Fig. 12.1a). He surrounded himself with bright protégés however, and soon others became interested in the chemistry of urine and stone disease. Lavoisier's meteoric rise as a scientific giant parallels the times in which he lived and died tragically as a result of another physician's invention, the guillotine. His influence and his laboratory methods were profound though his primary rival was Joseph Priestley (Fig. 12.1c) [9]. His interests were virtually all chemistry; sadly he did no basic work on calculi. His main assistant in the laboratory was Felix Vicq D'Azyr (1748–1794) who published a work on how animal concretions form in 1780 (Fig. 12.1a). He hypothesized that stones might form similarly from hyperconcentrated urine [10]. His influence in stone disease would come most from mentoring younger "chemists," helping them find interesting research projects. These included Antoine Fourcroy, Nicolas Vauquelin, and Joseph Gay-Lussac.

The Founders

Antoine F. Fourcroy (1755–1809) also experimented upon a large number of uroliths and tended to agree with the misconceptions of Scheele (Fig. 12.1a). Fourcroy is considered the father of clinical chemistry. He was born in Paris, son of an apothecary to the Duke of Orleans, and during his school days fell under the influence of Felix Vicq D'Azyr who convinced him to attend medical school [11]. He obtained his M.D. degree in 1780 and was attracted to the work of Lavoisier. By 1784 he was chosen as the professor of chemistry at the medical school. His initial interests were in biochemistry, specifically of bone disease, particularly rickets, and the relationship to stone disease. He discovered that "earthy stones" were made of calcium salts. He suspected that the underlying problem with rickets was with phosphoric acid metabolism [12]. His insightful investigations included questioning whether uric acid was confined to humans, if uric acid existed outside of the urine, how it was formed, and if there was any left in the urine after stone precipitated. He proposed and probably performed the first multicenter investigation of environmental and geographic regions to see if different stone types were seen in different areas. At the Societe Royale de Medicine in 1786, he had an open competition to compare stones and bones mineralogically [12]. In 1801 he published an 11-volume set on chemistry with 67 pages dedicated to and summarizing the current knowledge of stone disease. Fourcroy established the basic composition of uric acid and described calcium phosphate and magnesium ammonium phosphate stones [13]. He also wrote a treatise that stated that bladder and kidney stones were essentially similar. He organized his clinical colleagues around France to send him stones plus relevant data on the environment, geological information, and urine information. He eventually collected over 600 stones for his continued studies.

In 1802, Fourcroy published his extensive research on stone disease. He identified 12 constituents in stones (7 of these in human stones) [14]. These 12 species were as follows: uric acid, ammonia urate, calcium phosphate, magnesium ammonium phosphate, calcium oxalate, and animal matter (gelatin) or combinations of these. He believed that uric acid was the most common substance in stones. He classified these seven human constituents into three categories. One was uric acid and its sodium and ammonium salts. Second were mineral salts. Here he noted calcium phosphate, magnesium ammonium phosphate, and calcium oxalate. He stated that calcium oxalate was often the main component of kidney stones, and he also noted small crystals of this in human urine. He hypothesized that calcium oxalate might be the nucleus that begins accretion of all stones. His incidence of stone types was as follows: 25 % were predominately uric acid, 25 % were calcium oxalate, and the rest were mixtures. These numbers are eerily similar to modern series. He concluded his paper by speculating that oxalic acid was normally made somewhere in the lining of the urinary tract; this was wrong. Fourcroy and his colleague, Nicolas Louis Vauquelin, not only expanded the chemical properties of uric acid, they identified the sodium and ammonium salts. Fourcroy also pursued the therapeutic possibility of dissolving such stones and commented that only pure uric acid stones should be capable of being dissolved [4]. As noted earlier, the problems of the world at the turn of the nineteenth century enveloped the life and work of Antoine Fourcroy; the French Revolution not only shrouded his work in some degree of isolation, much of his clinical writings on stone disease were unknown in England. In addition, he became embroiled in the arrest and trial of Lavoisier. Being from the common populace and given his academic credential, he rose to the Council of Elders eventually, but first he served as a member of the convention that accused Lavoisier. The legendary comparative anatomist Georges Cuvier in his *Eloge historique* stated that there was nothing that Fourcroy could do to save his doomed friend [15].

William Hyde Wollaston (1766–1826) was another contemporary of these other investigators who also was interested in stone chemistry (Fig. 12.1c). William was born in East Dereham vicarage on August 6, 1766. He was a scholarly youth and picked up Greek, Hebrew, and Latin prior to matriculating to Cambridge. He was interested in all of natural history and turned to medicine. In 1789 he began to practice with an uncle at Bury St. Edmunds and was admitted to the Royal College of Physicians in 1795. He eventually moved to London where he wrote his first paper for the Royal Society in 1797 [16]. Wollaston further refined chemical techniques to investigate the properties of uric acid and also became an expert in crystallography. He noted, "*no opportunity of paying attention to any urinary concretions to which I could have access*." Wollaston was the first to identify cystine from the bladder of a 5-year-old boy. He differentiated this stone from uric acid and correctly identified the first amino acid [17]. The original stone has been subsequently reinvestigated with modern chemical methods and has been reconfirmed to be cystine [18]. Alexander Marcet became his pupil and would go on to describe a family with a history of cystine stones, thus identifying cystinuria. He published the most significant work on urolithiasis up to this time in 1797: *On Gouty and Urinary Concretions* [19]. In that year he presented to the Royal Society on the origin of stones. He identified five constituents as follows: lithic acid (does not know of Fourcroy's or Pearson's further work), sodium lithate (gouty matter), fusible calculus (it forms ammonia when melted), mulberry calculus (consists of both organic acids and oxalic), and calcium phosphate. The very next year, Pearson presented his findings using a collection of 300 stones [20]. Wollaston next went to work to advance the knowledge of crystals and crystallography. He advanced the science of studying crystals and invented a goniometer. He wrote letters with Mitscherlich on crystal theory. He also independently discovered magnesium ammonium phosphate crystals (coffin lids).

Wollaston was a restless and insatiable intellect. By 1800 he had decided to leave medicine to concentrate on basic science, and he became an early supporter of Dalton's atomic theory. In 1801 he purchased a house at 14 Buckingham Street and began an intense research that he guarded jealously. He identified a method of purifying platinum and for rendering it malleable. This alone made him a fortune. He wrote 56 wide ranging articles, 40 of these were read to the Royal Society. His reputation was such that his friends called him "the Pope" [17]. Wollaston became a founding member of the Geological Society along with eponymous James Parkinson. He died at the age of 62 in 1828 and bequested a year's income and a medal to one individual for his or her research "into the mineral structure of the earth." The geological medal still bears his name and was first awarded to William Smith. One final Wollaston caveat is essential. A little documented collaborative effort of his with his favorite pupil, Marcet tried to investigate an assertion by the eminent physician-poet Erasmus Darwin and his son Charles Darwin (not the evolutionist, though were all probably similarly disposed, but his uncle) on a hypothesized passage from the digestive system to the kidneys without involving the bloodstream in 1780 [21]. Wollaston conceived of an experiment where he gave potassium cyanide (yes, the poison) in carefully controlled non-harmful doses to patients [before institutional review boards (IRBs) and the FDA] and measured levels in the blood and urine using a Prussian blue test. He could not find any serum levels of cyanide, suggesting Darwin might be correct. He had Marcet confirm his findings and they hypothesized this might be the reason for sugar in the urine of diabetics but not in the blood.

It is amazing that in a rapid and very short period of time, in fact less than 40 years, a small number of truly amazing individuals solved the "*mystery of mysteries*" (Herschel) of stone disease. Almost all stones that humans routinely form (calcium oxalate, calcium phosphate, magnesium ammonium phosphate, uric acid, and the much rarer cystine) were all identified. Stone disease was no longer a simplistic matter. There were at least five types of stones that humans formed. Each type would have to be investigated separately to further elucidate the mechanisms of stone formation and specific therapies. Each of these giants of early medical chemistry would develop a legacy that would follow in their wakes. Each would develop a following in their respective countries. As the world devolved into chaos with the rise of Napoleon Bonaparte and the first truly world wars, the science of stone disease would continue but become increasingly isolated by language and countries. Yet advance it would.

The English School

A contemporary of Wollaston and his friend and pupil was Alexander Gaspard Marcet (Fig. 12.1c). He was born in Geneva to a successful merchant family with Huguenot lineage. He and his boyhood friend became involved in the French Revolution, and he was imprisoned but eventually banished from Switzerland for 5 years. He went to Edinburgh and studied medicine and chemistry with Cullen and Black. He graduated in 1797 and moved to London where he married the wealthy daughter of Swiss merchants, Jane Haldimand [22]. She also would become a renowned chemist, publishing her own book *Conversations on Chemistry* that became famous as one of the major influences of a then young Michael Faraday. They had a son, Francois, who would become a distinguished physicist [23]. Marcet adapted to the rigors of London and naturalized as an English citizen in 1800 where he lived and worked as a physician for 20 years. He secured a teaching post at Guy's through connections with William Sunders. He became involved with the Medico-Surgical Society of London and became the Foreign Secretary until his death in 1822. In this position he became friendly with the Swedish chemist Jöns Jacob Berzelius (1779–1848) who came for a visit in 1812. In fact, the famous chemist copied Marcet's plan of lectures with accompanying experiments for use in his own courses [22]. He also became significantly interested in teaching medical students chemistry at Guy's, and he prided himself in his abilities to perform microanalysis on substances and developed his own portable chemistry kit. Though personally Marcet was probably rigid and inflexible in his own perceptions, in the presidential address in the year of his death, Humphry Davy said of his work "*his different papers, published in the Transactions, on chemical subjects, show how capable he was of sound reasoning, accurate experiments, and ingenious views, in his department of science*" [24]. Marcet was dedicated to his patients and the hospital at Guy's. Davy also remarked that Marcet had "*warmth of manner, arising from a warmth of heart, which ensured affection*" [24].

Alexander was a physician and chemist working in London and obtained calculi from Norwich Hospital (1774–1842) which had one of the largest and busiest stone services in England. Yelloly would go on to analyze 1,500 urinary stones from the Norfolk and Norwich Hospital in the 1820s [25]. He was the first to discover xanthine stones, an extremely rare metabolic stone from the uric acid family of metabolites. Xanthine came from the Greek word for yellow, as Marcet noted a lemon-yellow color when this stone was treated with nitric acid. His friend Berzelius called it urous acid, but Justus Liebig (1803–1873) noted it lacked an atom of oxygen from uric acid in 1838. His book "*An Essay on the Chemical History and Medical Treatment of Calculous Disorders*" in 1817 was encyclopedic of the knowledge of stones at the time and underwent a second edition by 1819 [26]. Here he identified another unusual stone type, the fibrinous calculus. Marcet's book was hailed as the primary source on calculus and urine chemistry. Marcet gave practical tips to aid in the identification of the types of calculus disease. He was a medical nihilist suggesting that little could be done for stone disease. Quite in contrast to his predecessors who favored the soap and alkalis with their associated gastric and intestinal side effects. He actually was a proponent of surgery, though anesthesia and antisepsis were still future developments.

Marcet endeavored to develop a central repository for stone disease with pathologic specimens that could be analyzed and information about the patients' history and their diets which could be correlated to the stone analysis. He dedicated his magnum opus to his friend and mentor Wollaston. Marcet opened his comments by stating "*Physicians and chemists from Galen to Paracelsus to Van Helmont and Boerhaave were unable to form any rational conjectures on the composition of urinary calculi*" (12). He even proposed to start an international consortium using Berzelius. He illustrated his work with colored drawings and even showed his portable chemical laboratory for bedside analysis: "*I have thus pointed out the summary modes of analysis by which, with very little chemical skill or knowledge, and with an extremely simple apparatus, the various kinds of urinary calculi may be easily distinguished*" (122). In his text he described a detailed clinical history from patients. In another chapter he described his statistics from Norwich Hospital from 1772 to 1816 (44 consecutive years) and used this institution as a model for English centers. He extensively reviewed all relevant prior published investigations (including the French—difficult to get because of the war years) and notes again that hard water appears to reduce the risk of stone formation. He estimated surgical intervention at various London institutions over 10 years as follows: St. Tomas's 1/528 patients, St. Bartholomew's 1/340, and Guy's at 1/300. He compared this to the Parisian Hopital de la Charite at 1/250, giving our first international surgical rates. He concluded with a chapter on the medical therapy. He became extremely interested in the therapeutic use of mineral waters and was a leading investigator into various regions of mineral contents. Marcet retired from

Guy's and medical practice in 1819 when his wife inherited her father's vast estate but he still dabbled in chemistry. Interestingly, John Bostock took over his chemical lectures at Guy's, but Marcet had one more adventure in medical chemistry. He was asked to investigate a 17-month-old male infant whose urine was a deep purple color that turned black when exposed to the air. He had a junior colleague continue the chemical investigations, William Prout, who called it appropriately melanic acid (later named alkapton by Boedeker or homogentisic acid) [27]. Alexander John Gaspard Marcet died with a sudden illness referred to as "gout in the stomach" at age 52 [24]. Marcet set the bar for the founding fathers quite high and some of the British lineage would follow his trajectory to even greater heights.

William Prout (1785–1850) became a natural medical chemist to follow the Guy's Hospital legacy (Fig. 12.1c). He was born in Horton, Gloucestershire, in 1785, and he also studied medicine in Edinburgh and benefitted from Cullen and Black omnipresence graduating in 1811 [28]. He came to Guy's Hospital and fell under the influence of Marcet (and probably Wollaston). He married Agnes Adam of Edinburgh in 1814 and they had six children. He quickly left Guy's Hospital to develop his own private practice. He specialized in treating patients with urinary problems, perhaps one of the first urologists. His first clinical interest was in the urine of a boa constrictor on exhibition in the Strand. He found that its excrement was 90 % pure uric acid but formed no stones. He was elected a fellow of the Royal Society in 1819. He believed strongly that chemistry investigation could augment the knowledge of physiologic processes. He wrote a whole paper urging medical doctors to become physiologists and chemists. He became a proponent of Marcet's idea of a portable patient-bedside chemistry kit and created his own: "*These, with one or two small test tubes, and small stoppered phials, containing solutions of pure ammonia, potash, and nitric acid, can be readily packed into a small portable case, or pocket book, and will be sufficient, by the aid of a common taper or candle, to perform experiments on the urine, and urinary productions, that are commonly necessary in a practical point of view*" (200). His colleague at St. George's Henry Bence Jones would give Prout the honors of being the first to make the true connection between chemistry and medicine.

William published his major treatise on stone disease that would eclipse Marcet's in 1821 entitled, *An Inquiry Into the Nature and Treatment of Gravel, Calculus, and Other Diseases Connected with a Deranged Operation of the Urinary Organs* [29]. This work would go through five editions in his lifetime. He changed both the titles and the contents with time and further developments in chemical knowledge. He specifically documented that the acidity of the urine had effects upon the color and sediment of the urine. He also suggested the importance of knowing the 24-h volume of urine output. He looked for bilirubin discoloration on pure linen. He carefully measured the specific gravity of urine (if greater than 1.030 he suspected diabetes). He also was a therapeutic nihilist on the medical treatment of stone disease, similar to Marcet.

Prout is actually best remembered not for his contributions to stone disease but the chemistry itself. He was an early proponent of Dalton's theories and used integral atomic weights (whole numbers). He suggested that hydrogen might be the primary matter from which all elements were formed. He presented this shattering notion in two papers in the *Annals of Philosophy* in 1815 and 1816 [30]. He won the Royal Society's Copley Medal in 1827 for his work "*On the Ultimate Composition of Simple Alimentary Substances, with Some Preliminary Remarks on the Analysis or Organized Bodies in General.*" In this landmark work he was the first person to classify saccharinous (carbohydrates—he actually calls them "hydrates of carbon" though Carl Schmidt got the honors of naming in 1844), oleaginous (fats), and albuminous (proteins), though he also added a fourth primary category, water [31]. In 1831 Prout was elected to give the three Gulstonian lectures at the Royal College of Physicians. He waxed philosophical about the potential of chemistry to augment doctor's knowledge of physiology: "Chemistry, however, in the hands of the physiologist, who knows how to avail himself of its means, will, doubtless, prove one of the most powerful instruments he can possess." He like one of his younger Guy's Hospital protégés would add one admonition. He advised his colleagues to pay attention only to what is actually observed and to avoid visionary hypothesis [32]. Finally, Prout is also lionized for his isolation of hydrochloric acid in gastric juice (muriatic acid) in a paper read at the Royal Society of London on December 11, 1824, which was later confirmed by American surgeon William Beaumont on his famous patient Alexis St. Martin [33]. His later years were marred by progressive hearing loss. His textbook on stone disease was eclipsed by a young Guy's man, Golding Bird. He died of a sudden pulmonary illness in 1850.

Henry Bence Jones (1813–1873) was another physician-chemist who arose to prominence at St. George's Hospital (Fig. 12.1c). Henry was born on December 31, 1813, at Thorington Hall, Yoxford, in the county of Suffolk. He entered Cambridge's Trinity College in 1832 and thought to enter the church but changed his mind and obtained a position studying at St. George's Hospital as an apothecary in 1836. In 1838 he became a full-time medical student, and his interest in newly scientific methods was demonstrated by his use of the "stethoscope" with Dr. Hope on the wards [34]. He contracted rheumatic fever and had to interrupt his medical studies. While recuperating he took some chemistry studies with Professor Thomas Graham who happened not to be present, but his associate Mr. George Fownes was and had just finished training with Justus Liebig (1803–1873), a rising star in Germany (Fig. 12.1b). Henry wrote his first paper after the year in the lab with Fownes on cystine stone disease. He suggested that "*there may be two similar cystic oxide calculi, with one having more or less of its oxygen replaced by sulphur*" [35]. Bence Jones finished his medical education at St. Georges' in October 1840 and passed his examination in the spring of 1841 and was admitted as Licentiate of the College. He was off to Giessen and the swarming laboratories of Liebig to study animal chemistry (now organic chemistry).

Bence Jones arrived in Giessen at the height of Justus Liebig's fame. He learned at the bench techniques in analytical chemistry, quantitative methods of organic chemistry, and reactions of physiologically important biologic substances. He returned to the medical wards at St. George's in October and in the following May married his first cousin, Lady Millicent Acheson, daughter to the second Earl of Gosford. He went to Cambridge and picked up an M.A. degree on his work with Graham and Liebig and was back at St. George's by October. In December 1845 he was appointed as assistant physician at St. George's, and within just a few months he was able to fill a vacancy as a physician, a meteoric rise [34]. Bence Jones was a bit overwhelmed and wrote in his autobiography: "*In this alliance I had formed in the shop became my greatest support in the wards of the hospital, and I rapidly acquired knowledge in the management of the patients and confidence in myself, though my private practice was very small indeed for some time. Gradually, however, my chemical knowledge brought me medical men to ask for my opinion on their own cases, and this was followed by their occasionally bringing me their patients for consultation*" [36]. Bence Jones soon attracted patients that included the leading lights of his time: Thomas Huxley, Charles Darwin, Herman von Helmholtz, A.W. Hoffman, Herbert Spencer, and ultimately Benjamin Disraeli. He was a lifelong friend and physician to Michael Faraday and eventually became his biographer. Florence Nightingale became a friend, and she regarded him as the best "chemical doctor" in London [34].

Bence Jones was asked to analyze and catalogue the calculi in the Museum of University College Hospital which he did. Jones published his first book "*On Gravel, Calculus, and Gout; chiefly an Application of Professor Liebig's Physiology to Prevention and Cure of those Diseases*" in 1842 [37]. In this context, Bence Jones used Liebig's concept of oxidation to explain the formation of stone disease. The increased oxidation of uric acid to the more soluble urea, while simultaneously blocking the breakdown of muscle, was the primary pathway to stone formation. Liebig believed that the oxidation of uric acid in the body yielded urea, oxalic acid, and CO_2. Jones proceeded to suggest that increasing the oxygen supply to the body by exercise and controlling the intake of both nitrogenous and non-nitrogenous foods might be beneficial. He also recommended using alkaline medications to keep the uric acid in solution where it could be oxidized more in the blood. Bence Jones arranged his book into two parts, the first concentrated on uric acid stones and gout though he included eight chapters that covered most known stones. In the second part he talks more generally about stone formation and treatment. He avoids significant discussion on surgery. Jones's book was widely criticized because of its laudatory nature towards Liebig and his theories. There were pearls of knowledge present however, including his noting that oral ammonium salts produced acidic urine which might be helpful in some stone patients. Bence Jones was the first person to describe the xanthine crystal in urine and differentiated it from uric acid crystals. Possibly owing to his close relationship to Michael Faraday at the Royal Institute, Jones also became interested in electrolysis. He attempted some rather interesting experiments to see if an induced electrolytic reaction might enhance the ability to break down bladder stones [38]. Bence Jones died from complications of rheumatic heart disease that he was able to diagnose himself with his stethoscope. He is best remembered from his eponymous protein markers found in patients with multiple myeloma, Bence Jones proteins, which he described in 1848 [39].

Richard Bright (1789–1858) might just be the most well-known physician in this select group of founding fathers, but he also contributed the least to our knowledge of stone disease, though he is considered the father of nephrology (Fig. 12.1c) [40]. In addition, he became the mentor and model physician for a whole generation of physicians. Two of his protégés will follow in this presentation, Drs. George Owen Rees and Golding Bird all who practiced at Guy's Hospital. Bright was interested in stone disease early in his career, but this soon gave way to his interest in medical kidney disease. Richard Bright developed the first ward metabolic unit in the world to investigate renal diseases and to separate renal dropsy (edema) from other causes (cardiac and hepatic) [41]. He attracted bright, young, and talented physicians to his cause. He introduced a clinical laboratory on his unit to pursue urine and blood chemistries and hired George Owen Rees who would become a lifelong friend of Bright, and they added the spoon for identifying albumin in urine of patients with kidney disease. Bright established a team that carefully documented and followed each of his patients on the special 42-bed unit. His first collaborator was the chemist John Bostock. Others included George Hilaro Barlow, Rees who we've just mentioned, George Robinson, and Frederick Pavy [42].

George Owen Rees (1813–1889) was born in Smyrna, Turkey, in 1813 where his father was a successful Welch merchant (Fig. 12.1c). He entered Guy's at the age of 16 as pupil of Richard Stocker, an apothecary. Richard Bright recognized this gifted youth's potential, and he was engaged in his team from 1833 when he was just 20 years old [43]. Rees became in charge of all the chemical work on this experimental ward and wrote his "*On the Analysis of the Blood and Urine, in Health and Disease. With Directions for the Analysis of Urinary Calculi*" in 1836 [44]. Rees's goal was not to reproduce the efforts of Prout or Marcet but to develop simpler and easier to use methods for medical practitioners. He begins "*Since chemists are not physicians, we shall scarcely benefit by their art, except by making the physician a chemist*" (35). Rees did not add much more to the knowledge or treatment of stone disease though he became lifelong friend of Richard Bright. He dedicated his second edition of *On the Analysis* to his mentor. He became a founding member of the Chemical Society [4]. Rees contributed mightily to our chemical understanding of kidney diseases and became a fellow of the Royal Society. In the Lettsomian lecture at the Royal Society of Medicine, he challenged his junior colleague at Guy's Golding Bird on the nature of oxaluria. This is one of his few errors where he leaned upon the suppositions of Bence Jones and Liebig. Rees lived the life of a club bachelor; he was a gourmet and smoked fine cigars at the best clubs in London. George ultimately became Physician Extraordinary to the Queen and died from a cerebral hemorrhage on May 27, 1889 [43].

The English school of physician-chemists contributed massively to our understanding the basics of this ancient malady stone disease. There is no way to include everyone that played a role in this story and there is no clear separation of these individuals into actual groups. But nationality and hospital based associations made for a convenient method to categorize them. This is not so apropos to the discussion of the French and European contributions which were also substantial. The chaos that followed the French Revolution and the First and Second Empires make them less tidy or harder to cubby hole into narrative. In addition, some of these works have never made it to an English translation, thus unavailable to nonlinguistic scholars.

The French School

Nicolas Louis Vauquelin (1763–1829) represents the scholarship and deep interest in the study of stone disease (Fig. 12.1a). His contributions were perhaps even more significant than his mentor's Fourcroy. He came from a modest background, born in Normandy. He came to Paris at 21 to become an assistant in pharmacy but developed a passion for chemistry via a cousin in Fourcroy's laboratory [45]. His work with his mentor lasted until Fourcroy's death in 1809. The rigorous method of experimental pursuit by these early investigators included experiments and dissection of various animal species. They noted that man was the only mammal to form uric acid stones. Pearson and Vauquelin could not find uric acid stones in large carnivores (lions and tigers) [46]. Vauquelin followed up these observations by confirming a lack of uric acid stones in the horse, cow, rabbit, dog, cat, pig, and rat. Vauquelin noted that the exterior and cut appearances of stones were predictive of their chemical composition. Nicolas followed up on this by describing the concentric laminations of many stones (more on this in Liesegang rings), offering the appearance of onion-like lamella loosely held together. He noted that many uric acid stones were not fully soluble in alkali because they were not pure uric acid. He wrote four papers on animal stones and he concentrated much effort on these discussions. Nicolas was perhaps the father of animal stone science. He was the person to confirm Pearson's observations that uric acid stones appeared to be confined to humans; he did not know about Dalmatian dogs. Vauquelin also found that bird's excrement was almost totally uric acid. He studied the diet habits of animals and the stones he studied. Vauquelin noted that horses, cows, and rabbits have carbonate stones. He noted that dogs, cats, pigs, and rats have calcium and magnesium ammonium phosphate stones but rarely calcium oxalate stones. He further hypothesized the there was a large amount of magnesium in some cereals fed to these animals [45]. Nicolas Vauquelin was always the second author on many of these papers, but he essentially did all of the benchwork chemistry. Fourcroy had risen in the ranks of government service while Vauquelin persisted in the lab. He became the head of the Faculté de Pharmacie de Paris which maintained until he died. He was removed with ten of his colleagues from the medical school in 1822 after having isolated chromium, beryllium, nicotine, asparagines, and quinine [45].

Francois Magendie (1783–1855) often better known as the mentor of Claude Bernard put forward the argument that depending on the stone type, a patient might benefit from urine that is either alkaline (for uric acid and cystine stones) or acidic (for the remainder) (Fig. 12.1a). He also first noted that reduced protein intake should lower the content of urinary solutes and decrease the risk of stone formation. His own editors F. Arago and L.J. Gay Lussac sadly noted that these recommendations would be hard for medicine to accept [45]. They were prophetically correct. He is now most well known as a pioneering physiologist [47].

Pierre Francois Olive Rayer (1793–1867) pioneered work on urinary crystals (Fig. 12.1a). He was born in Saint Sylvain near Caen in 1793. He went to Paris to study medicine in 1812 and became interested in anatomy, chemistry, and clinical medicine. He was a student of André-Marie

C. Duméril and became interested in comparative pathology [48]. Rayer became embroiled in the political upheavals of his times but was an honored physician and did most of his work at l'hôpital de la Charité. He became interested in renal disease and published his "*Traité des Maladies des Reins*" in 1839 which was accompanied by an atlas with colored plates [49]. Pierre was an outspoken proponent of the use of the microscope, and he paid significant attention to crystal morphology associated with stone disease. His associate, Eugéne Vigla (1813–1872), set up the first routine use of urinary microscopy and correlated this with health and disease. Vigla and Rayer literally wrote the textbook of clinical urinalysis through the 1830s [50]. His final article on stones was a written collaboration with some of his many students, Die Krankheiten der Nieren und die Veranderungen der Harnsecretion, in 1844. He left the field of renal disease and became increasingly interested in infectious disease and bacteriology.

J.L. Prevost and J.B. Dumas will be the final French school scholars in this section on founding fathers. Jean-Baptiste Dumas (1800–1884) is the better known of the two and was born in Alès (Fig. 12.1a). At the age of 16 he moved to Geneva where he studied physics, chemistry, and botany prior to moving to Paris. He was befriended by Alexander von Humboldt and became a professor of chemistry at the Lyceum and later at the Ècole Polytechnique [51]. Though not so well known now, his is one of the 72 names inscribed on the Eiffel Tower. He did extensive work on the chemistry of the kidneys and was the first to show that they removed urea from the blood. He performed bilateral nephrectomies showing that there was rapid and continued rise in ureas. He did some pioneering work on attempting to dissolve bladder stones with his colleague Provost using electrolytic methods [52].

Golding Bird

Golding Bird (1814–1854) is the final though not certainly the only physician-chemist from this era at Guy's Hospital (Fig. 12.1c). Bird has been pulled out of context with the rest of the researchers here for several reasons. His book on stone disease is singularly different. He adds microscopy like Dumas and discusses historical precedents like Marcet. He is at heart a chemist, like Prout, yet notes the pathology of the kidneys like Bright, Rees, and Rayer. Finally, Bird also explored the theoretical realms of chemistry and physiology more like Bence Jones and his mentor Liebig but more open-minded. In this fashion he is more like Rees and questions the "fallacy of theories" especially to Liebig's overall animal chemistry [53]. He likely was substantially influenced by Marcet, Prout, Astley Cooper, Rees, and Bright. But he dedicated the first edition of his book about stone disease to his great medical mentor: Thomas Addison [54]. He was born at Downham in Norfolk on December 9, 1814. His father was a successful bureaucrat and his younger brother Frederick also became an outstanding physician and eventually diagnosed his brother's terminal illness as rheumatic heart disease. He was always sickly but pushed himself very hard. Bird is also special as he died of septicemia and urolithiasis in addition to his rheumatic fever.

Golding matriculated to Guy's Hospital at age 17 in 1832. He came to the attention of Dr. Addison and Mr. Astley Cooper. Cooper in fact asked the bright young man to help in his investigations of the female breast, and he subsequently authored portions of Cooper's textbook. His first student paper was published questioning some findings of Prout's on uric acid and purpuric acid which Prout duly responded [54]. He graduated in 1836 and was awarded the license of Apothecaries' Hall without examination and with honors. He established a private practice and had several offers for appointment and took one at Finsbury Dispensary. In 1836 he was appointed lecturer at Guy's and took up electrical medicine. His first book for medical students was *Elements of Natural* Philosophy which went through many editions and became popular with students: "*The very liberal amount of support that this work received has induced the author to entertain a deep sense of his own responsibility to science, and in the preparation of this edition to seek* *further assistance by association with himself a coadjutor*" [55]. Bird had his friend Charles Brooke help in the fourth edition of this popular work. He became a lecturer on materia medica with his mentor Dr. Addison. He became a member of the Linnaean, Geological, and the Chemical societies and finally a fellow of the Royal Society: "*That now a field was opened to his indomitable energy, and he left nothing unheeded, no hour unemployed. Each day had is appointed work; the early morning saw him attending to the sick poor who thronged to his house; his private professional engagements and literary labours engaged him til evening; and many hours of the night-often, too often, the entire night—has passed in unbroken study*" [56]. Bird became interested in urinary and stone chemistry from his early days at Guy's Hospital.

Golding Bird dedicated a large portion of his research interests into the study and chemistry of urinary stone disease. Throughout the early 1840s he published numerous accounts on the studies of urine, stones, and crystals. He utilized the microscope and detailed the various crystalline phases leading to stone development. His papers were frequently illustrated by magnificent sketches of crystals. He also had come to the opinion that the nucleus of stones represented their formative identity within the kidney. Once the stone's nucleus had formed, the urine itself provided the ability of crystalline growth. He had as his reference 342 stones from the collection at Guy's Hospital, possible through the intervention of Cooper. He labored in evaluating each stone from its core or nucleus outwards through its various layers [57, 58]. He concluded that there were seven *genera* of stones that depended upon their nuclear composition. Each *genus* could be subdivided into various other species following the theme from biologic taxonomy [57, 58]. He wrote his magnum opus "Urinary Deposits, their Diagnosis Pathology, and Therapeutic Implications" which also became very popular and went through at least five editions and one revised edition [57, 58]. This is the textbook that displaced Prout's and Bence Jones's works. This work also attracted a French translation of numerous British works.

Bird also introduces the students of stone chemistry to the notion that uric acid is the most common stone type but that calcium oxalate stones are also very common. This is the first real step towards modernism (though current trends show a rise again in uric acid stones typically associated with rising obesity). He makes a broad generalization that all the stone types probably represent two major classes, organic (such as uric acid and oxalic acid stones) and inorganic stones, which leads him to the notion of Liebig and vitalism. Bird was attracted as were many physicians to the notion of chemical equations of organic compounds could be balanced showing derangements in physiology. He made a great deal about the balancing of carbon, oxygen, nitrogen, and hydrogen atoms in stone types. The difference between Bird's and Bence Jones' notions was a much greater degree of skepticism towards the process of stone formation. Although he found much about the balancing of atoms attractive, "*but who shall dare to state that the great and mysterious agent presiding over the chemistry of the animal body proceeds in such a manner?*" [57, 58]. Bird remained squarely aligned with the more standard Berzelius theories of chemistry and would not render the assumptions that entrapped Bence Jones. Golding Bird lived a prolific but short life, dying at the age of 39 on October 25, 1854. He was impaired by rheumatic fever but most likely dying from sepsis and stone disease: "*By the month of October it was evident that his case was a hopeless one. Nausea, vomiting, oedema of the feat and face, hematuria, pyelitis, and vesical pain, all indicated that life was drawing to a close*" [56]. He left a wife with five young children.

Discussion

Alex Copland Hutchison was another surgeon who wrote a treatise on stone disease on May 4, 1830, entitled "*A Further Inquiry into the Comparative Infrequency of Calculous Diseases Among Sea-Faring People, with some observations on their frequency in Scotland*" [57, 58]. In this published review, Mr. Hutchison discussed the trend for decreased incidence of stone formation in sailors in the British Navy. He utilizes the chemistry work of the founding fathers, especially Marcet's and Prout's theories to speculate on this interesting phenomenon. In addition, he goes further by surveying some of his fellow surgeons all around England and Ireland to come up with some basic numbers of stone patients in port cities. He compares the incidence in Dublin to the incidence of stone disease amongst Roman Catholic priests and quotes a study by Dr. Egan from the Transactions of the Royal Irish Academy. All of this data is distilled into one table (p. 118) of his treatise summarizing his peculiar comment: "I *feel assured, indeed, with my lamented friend, Dr. Marcet (recently died), that it is chiefly in this way that the true pathology of the disease can ever be obtained, and, consequently, the most efficacious mode of treatment*" (120).

This work can and should be contrasted with John Greene Crosse's "*A Treatise on the Formation, Constituents, and Extraction of the Urinary Calculus*" [59]. This was published in 1835. Crosse was another surgeon who was interested in the science of medicine and in stone disease in particular. He was born on September 6, 1790, in Suffolk. He became one of the leading surgeons at the notorious Norfolk and Norwich Hospital which had the highest incidence of stone disease in England. This institution had the largest collections of stones for analysis. He also was elected as a fellow in the Royal Society and his son wrote a biography about his father [60]. His book on stone disease was originally an essay that won the Jacksonian Prize for medical writing by the Royal College of Surgeons in London. He thoroughly reviewed the fundamental chemistry that has been discussed throughout this section. He organized his work into 12 chapters that presented the different chemical types of stones, the proposed mechanism of growth, and the origins in the kidneys and then diverts our attention to the surgical aspects as might be expected from a surgeon. He unlike many others, however, pointed to many of the problems of current surgery including the reliance on poor diagnostic methods, such as sounding. He spent one entire chapter, Chap. 7 "*Of Sounding for a Stone in the Bladder*," on the problems associated with this inaccurate art (57). His efforts were not so much interested in statistics and incidence of disease but on causes and treatments. He was a surgeon who wanted to know why his patients were suffering and what he could do to lessen this suffering. He used all of the most current science that was streaming out of academic institutions such as Guy's Hospital, but Crosse demonstrated more than thorough acquaintance with foreign investigators as well.

Also the first major effort from an American author included Samuel D. Gross's "*Practical Treatise on the Diseases, Injuries, and Malformations of the Urinary Bladder, the Prostate Gland, and the Urethra*" in 1851 [61]. Samuel D. Gross was the surgeon that was immortalized by Thomas Eakins' "*The Gross Clinic*" painting of 1875. Gross was a pioneering experimental surgeon who rose in fame at the frontier school the Louisville Medical Institute. He practiced surgery there for 16 years before he was lured back to Philadelphia as the professor of surgery at Jefferson Medical College [62]. Gross was historically minded and the first to popularize Kentucky pioneering surgeon Dr. Ephraim McDowell and the removal of a bladder stone from the future president James Knox Polk. Gross's textbook has the beginnings of a modern urologic primer. It was not solely devoted to stone disease. Chapters 8 and 9 call our attention as these are devoted to stone disease. Gross displays a vast array of knowledge from international sources, and his first table is the age distribution for stone in 8,574 patients from England, India, the USA, Moscow, and France (166). He quotes original sources on rare knowledge of stone disease from Egypt and Professor Reyer as well as from Livingstone on Central Africa (168). He is taking stone disease very seriously. He discusses all of the important advances in stone chemistry and presents his table of 1,613 stones in Philadelphia and compares the stone types at other institutions and around the world (172). Differences in the incidence of uric acid and calcium oxalate stone types leap out at the reader. Cystine and xanthine stones are notably very rare. He like his surgical counterpart in England spends a good deal of discussion on the art of sounding prior to discussing surgical interventions as well. Gross's son Samuel W. Gross would follow in his father's footsteps and become a well-known surgeon at the Philadelphia Hospital [62]. He married Grace Linzee Revere, granddaughter of Paul Revere. Gross died at the tender age of 52, leaving the widow Gross. Osler was called in to care for the terminal Dr. Gross who had septicemia in April of 1889 just as he was leaving Philadelphia to become the professor of medicine at the new Johns Hopkins Hospital. Grace in turn married this young rising superstar of medicine who would write the definitive textbook of medicine and pioneered a new medical education in the United States and became the soul of the profession of medicine for decades, William Osler [63].

It is fitting to end this chapter on the founding fathers with Sir William Osler. He is such an enigmatic figure in the history of medicine. He did not really discover anything of great significance, but he had a well-endowed sense of humor with a childish tendency for practical jokes [64]. Yet he was loved by his patients, enshrined by his students, became an influential proponent for medical humanism, and an ardent bibliophile and historian of medicine. His parting address from the University of Pennsylvania has become an enshrined treatise in medicine "*Aequanimatias*" [65]. His vastly influential textbook, *The Principles and Practices of Medicine*, was an outstanding summary of the knowledge of stone disease at the end of the nineteenth century [66]. It is fitting that he too suffered from stones but this will have to wait for a later chapter. Osler best sums up the knowledge of physicians at this time, poised with so much knowledge, but just lacking key pieces to truly help the patients: "*The physician without physiology flounders along in an aimless fashion, never able to gain an accurate conception of disease, practicing a sort of popgun pharmacy, hitting now the malady and the patient, he himself not knowing which*" [67].

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13 Famous Stone Sufferers

Introduction

The literature is strewn with the flotsam and jetsam of diatribes regarding the cause and effects of urolithiasis. But in the final accounting of disease, human beings contract and suffer individually. An investigator deals with statistics, and patient lists generate clinical series. Often overlooked is the individual. It is almost impossible to write a scientific paper any longer about an individual without crossing the threshold of impropriety or now federal legislation concerning HIPA violation (Health Insurance Portability and Accountability Act of 1996, Public Law 104–191). Yet the individual is the unique endpoint of all discussions of disease, the final common denominator between treatment and outcome. So it behooves those whose mission remains to become knowledgeable about stone disease to have at least passing knowledge of a catalogue of the only patients one can discuss outside of these realms of impropriety and Federal jurisdiction, those suffering that are already famous. Our society has already bypassed the acceptable boundaries of this indiscretion for a more tabloid notoriety. This represents an attempt at scholarly, chronologic listing of famous urolithiasis sufferers. Since I've first written this portion and presented it to a group of urologists, there has been subsequent substantial interest in this on the Internet. I have incorporated this author's endeavors to make it more complete, though, no doubt, there are others that are missing [1, 2].

The Legacy of the Famous Stone Patient

The Internet and historical literature regarding urolithiasis provide the student of history a list of famous stone sufferers [2–12]. Any cross-referenced confirmation of these patients' stone suffering was then traced. If there is identified confirmatory information from secondary sources, they were included in this list. Recognizing that, the list, no matter what details could be found, is likely to be incomplete. But then, adding to the list will fall upon the shoulders of others in the future. The particular emphasis was upon science writing and articles from the past, as the modern current literature suffers from society imposed necessity, to limit identification of the stone sufferer. In this article, there will be no emphasis on the suffering or treatment of these people. The purpose is to just generate a single list, as comprehensive as possible of famous stone patients.

Famous Stone Patients

The following table represents the verifiable list of famous stone patients. They are classified by the category or profession that each individual would be most identified. For some members of well-known stone patients such as Ben Franklin, he could be in several categories (but selected here as physicians, because of his particular medical interests in stone disease). In addition, in

M.E. Moran, *Urolithiasis: A Comprehensive History*, DOI 10.1007/978-1-4614-8196-6_13,

each classification, they are listed in chronological order.

Pre-Christian Era: Mesolithic woman, El Amrah boy age 16 dated about 4,800 BC. (Prof. G. Elliott Smith in Hunterian Museum) first known stone former, Epicurus (270 BC).

Philosophers/Scientists: Erasmus of Rotterdam, Michel de Montaigne, Francis Bacon (and his brother), Galileo, Sir Isaac Newton, Gottfried Leibniz, George-Louis Leclerc (Comte de Buffon), Robert Boyle, Benjamin Franklin, Horace Walpole, and Isaac Asimov.

Physicians: Hermann Boerhaave, Johan van Beverwijck, Thomas Sydenham, Antonio Scarpa, Benjamin Franklin, Thomas Linacre, William Harvey, Saint Nicholas Steno, John Jones, Philip Syng Physick, Sir William Osler, and Richard Selzer.

Authors: Isaac Asimov, Samuel Pepys, Michel Montaigne, Mary Ann Evans (George Eliot), Llewelyn Powys, Jack London, Ethel Wilson, Isaac Asimov, Kevin Murphy, Chuck Palahniuk, Art Buchwald, Sir Walter Scott, David Sedaris, and Horace Walpole.

Clergy: Pope Vigilius, Saint Aelred of Rievaulx, Martin Luther, John Calvin, Cardinal Mazarin, John Wilkins (English clergyman), Pope Innocent XI, John Wilkins, Pope Clement XI, Mary Baker Eddy (Christian Science founder), Billy Graham, Mother Teresa (perhaps one of her miracles), and Bishop David Zubik.

Leaders: Caesar Augustus, Henry II of Bavaria, Frederick III (King of Saxony), Dom Pedro I of Brazil, Empress Anna of Russia, Peter the Great, Louis XIV, Oliver Cromwell, Sir Kenelm Digby, James I of England, John Marshall, King George IV, John Hart (signer of the Declaration of Independence), Napoleon Bonaparte, King Leopold I of Belgium, Napoleon Bonaparte, Napoleon III, Nicias (leader of Athenian Army), Lord Cochrane, Lyndon Johnson, Dennis Hastert (House Speaker), John Prescott, Mäori Queen Dame Te Atairangikaahu, Myles Standish (Plymouth Colony), Robert Walpole, John Hart (Continental Congress), General James Wolfe, James Knox Polk, Colonel Edward M. House, Indira Gandhi, President Sukarno (Indonesia), Ratko Mladić (Serbian commander), Senator John McCain, Representative Tom Price, Representative Mike Simpson, Ted Kennedy, and Peter Mandelson (British politician).

Artists and Musicians: Ludwig van Beethoven, Michelangelo, Giovanni Gabrieli, Alan Ginsberg, Arthur Sullivan, Bing Crosby, Cole Porter, Brigit Nilsson, Charles Strouse, Peter Andre, Nick Drake, Billy Joel, and Adam Young.

Entertainers: Ava Gardner, Alfred Hitchcock, Lew Wasserman, Gay Talese, John Derek (husband of '10' Bo), Suzanne Strempek Shea, Roger Moore, Burt Reynolds, William Shatner, Tito El Bambino, Karl Pilkington, Bill O'Reilly, Kevin Murphy, Karl Pilkington, Buzz Kilman, Jamie Kennedy, Rob Schneider, Kiefer Sutherland, and Mike Vogel.

Athletes: Bob Hoffman (weightlifting), Joe Mauer (baseball), Bill Parcells (football coach), Sir Ranulph Fiennes (Antarctica explorer), Bruce Jenner (Olympian), Phil Jackson (basketball coach), Davis Love III (golfer), Bernhard Langer (golfer), Ian Holloway, Luiz Felipe Scolari (coach), Rafael Benitez (coach), Mark Recchi (hockey), Tony Gwynn (baseball), Dennis Cook (baseball), Ozzie Guillen (baseball coach), Rich Aurilia (baseball), Mike Cameron (bb), Derek Bell (bb), Tony Fernandez (bb), Bobby Jenks (bb), Whitey Kurowski (bb), Bill Mazeroski (bb), Tom Niedenfuer (bb), Miguel Olivo (bb), Jay Payton (bb), Brian Roberts (bb), Tim Salmon (bb), Joe Saunders (bb), Josh Willingham (bb), Robin Yount (bb), Jim Otto (Double Zero-football), and Bart Giamatti (Yale president and Commissioner of Baseball).

Fictitious TV/Movie Characters: Cosmo Kramer (Michael Richards) "The Gymnast" 6th episode of *Seinfeld*, Joey Tribbiani (Matt LeBlanc) of *Friends*, Al Swearengen (Ian McShane) in TV series *Deadwood*, Muddy Waters in an episode of

Family Guy, Duckman (from the cartoon *Duckman*), Brock (TV series *Reva*), and Maxwell Klinger (xx) in *M.A.S.H*.

Discussion

From the very earliest records, humans have been plagued by urolithiasis. There are no known ancient manuscripts that document individuals who have suffered, but the first known instance comes to us from Diogenes Laertius regarding the philosopher, Epicurus. His stone disease would result in loss of life. Some histories describe that the stone disease itself had affected the outcomes of wars, as in the case of Napoleon III. Others have had their suffering transformed into miraculous cures requiring sainthood (Saint Henry of Bavaria). Some have taken the desperate route of surgical lithotomy and lived to tell about it (Pepys and Marshall). Others braved the knife but were not so lucky, Leopold of Belgium. Stone sufferers have publicly aired their sufferings, which represent a literary legacy that has seldom been mentioned at stone meetings. Some writers have brazenly described their suffering from colic in magazines such as *Esquire* or in reference to their works (Alan Ginsberg and Richard Selzer) [1]. The notion of the stone patient's suffering that has most recently become a somewhat *cause célebre* might be illustrated by the fictional characters that have been cropping up on sitcoms and TV shows, including Kramer from *Seinfeld* and Joey from *Friends*.

Whatever the interest in urolithiasis at science meetings, the focus is rightly on pathophysiology, preventative strategies, incidence, therapeutics, and surgery. But the lessons of the past should not be forgotten, and the legacy of the individual might yet be introduced by knowledge of those who have suffered. Famous stone sufferers do not lead us to the knowledge that will change the disease, but their legacy should not be lost.

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14 Frederik Ruysch's Fascination with Urolithiasis

Introduction

> "*Mortuus, arte Tua, Ruyschi,*
> *vivit, docet, infans,*
> *Elinguis loquitur, mors timet*
> *Ipsa sibi*" [1]
>
> —Denis Papin

"*Trough thy art, O Ruysch, a dead infant lives and teaches and, though speechless, still speaks. Even death itself is afraid.*" The history of urolithiasis consists of many eras of varying scientific interest both medically and surgically. Along the pathway to our modern understanding of this disease lie the flotsam and jetsam of some various curious practitioners. People have made names for themselves as specialists in lithotomy in order to promote their fame (and increase their fees). Others have donned religious attire and monikers in order to increase their trustworthiness. One other practice, typified by itinerant lithotomists, was to collect stones from patients and carry them about, demonstrate them, in order to show the prowess of the practitioner. Perhaps the most macabre use of human stones was by the famed anatomist and surgeon of the seventeenth- and early eighteenth-century Amsterdam, Frederik Ruysch (1638–1731). This is a historical review of what we know about Ruysch to better understand his utilization of human stones as adornments, decorations if you'd prefer to his elaborate menageries. Ruysch was by all accounts a stellar medical practitioner, a gifted surgeon, a good lithotomist, and an outstanding father [2]. His legacy was both his written works but more significantly his outstanding anatomical and amazing artistic creations utilizing natural materials to make ethereal displays that remain hauntingly striking into our modern era.

He practiced mostly in Amsterdam during the golden era of the Dutch Republic. Rene Descartes (1596–1650) had matriculated to the more tolerant Dutch society out of fear for his opinions regarding science from the Catholic France and in the wake of Galileo's persecution in Italy. He had published his profoundly influential *Discourse on Method* in 1637 [3]. Descartes' theories of man as a machine, the notion that animals lacked souls, and his notion that all theories could be checked by study led to the rise of experimental work throughout the lowlands and the rise of vivisection and experimental anatomy especially at Leiden (Fig. 14.1a). Most of Holland had removed the shackles of the Catholic faith and had switched to Protestantism, especially the Calvinist type. Ruysch would use his special talents for anatomical preparation and display to moralize as well as teach.

Ruysch's Life and Times

> "*Homo sum: humani nil a me alienum puto.*" [4]
>
> —Terence

"*I am a man, and nothing human is alien to me*" said the Roman playwright Terence [4]. This is a fitting introduction to a master anatomist and creator of anatomical museums of the seventeenth

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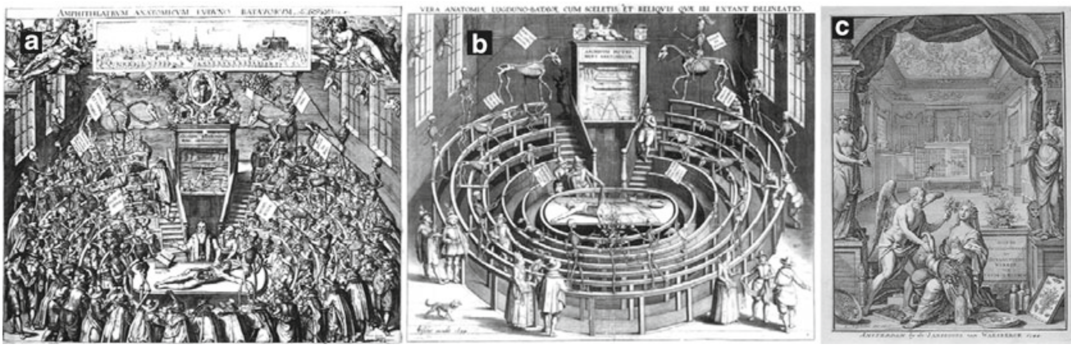

Fig. 14.1 (**a**) The famous anatomical theater at Leiden. (**b**) The same without all of the spectators to show more detail of anatomical displays. (**c**) Ruysch's museum in Amsterdam from the frontispiece of Ruysch, Alle de Werken [42]

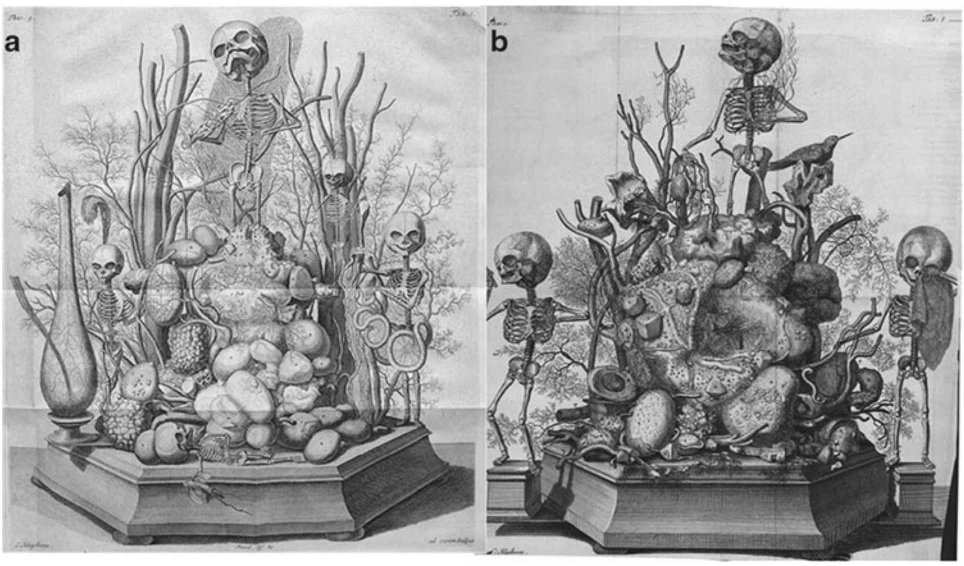

Fig. 14.2 (**a**) This is one of Ruysch's uses of human uroliths [3]. The illustrations were drawn by C.H. Huyberts. This is the musical "*Allegory of Death*." (**b**) Another vanitas utilizing human stones and assundried human membranes and vasculature

and eighteenth centuries, often called the Baroque period of art and music. This was the time of Handel and Bach in music. The sculpture of Bernini in Rome and the Golden Age of painting in the Netherlands with Peter Paul Rubens and Rembrandt were artistic examples of baroque styles in sculpture and painting [5]. The term formally started at the Council of Trent in 1600, and the notion was in part responding to needs for internal reform and implies "*a rough and imperfect pearl*" (OED). This same ideal could easily be applied to anatomy and the anatomist's art as we shall see. Review of published works of Frederik Ruysch included Dutch archival materials of biographical nature and his published catalogues of his anatomical collection [6, 7]. In 1691, Ruysch began to publish a catalogue of his collection of anatomical works entitled "*Frederici Ruyschii Thesaurus Anatomicus*" with illustrations by C.H. Huyberts [7]. This work is now available in an online electronic version for close scrutiny of the anatomical specimens. Of the works most pertinent to this writing, the human stones, there are no surviving specimens. The illustrations by Huyberts are the only remaining primary source of his utilization of human uroliths (Fig. 14.2). Descriptions by Ruysch and others suffice for this historical review. Particular attention was given to his illustrations and description utilizing human stones for artistic reality.

Frederik Ruysch was born on March 23, 1638, in The Hague. His father Henry Ruysch was secretary to the States General but died in 1654 [8]. Frederik's mother, Anne van Berghem, had to look after six children, and Frederik had to become apprenticed to an apothecary named Uylhoorn. He matriculated to the renowned University of Leiden and studied medicine from 1661 to 1664. He apparently was fascinated by anatomy and anatomical research and probably became very well acquainted with the famed anatomical vanitas, or anatomical demonstrations (Fig. 14.1b). Johannes van Horne (1621–1670) was the famous anatomist during his tenure. In addition, during his student years he was in a class of future superstars that included Jan Swammerdam (1637–1680), Niels Stensen (1638–1686), and Regnier de Graaf (1641–1673). De Graaf became a close friend of Ruysch and they subsequently spent a great deal of time together working on pathologic specimens [8]. De Graaf has been immortalized by naming the ovarian follicles after him. Professor van Horne was most impressed with Ruysch and he was very highly regarded in the medical school. His graduate thesis was entitled *De Pleuritide* on pleurisy. In addition, during his postgraduate period van Horne approached Ruysch to tackle a complex debate regarding the lymphatics and the liver. His injection methods of demonstration ultimately proved that the lymphatics indeed had valves [9]. Upon his graduation in 1664, Ruysch married the daughter of famed architect in Amsterdam, securing an influential circle of friends. In 1665, Ruysch became the praelector of the Amsterdam surgeon's guild following in the luminous pathway of Tulp and others. This appointment allowed him legal access to dissection of corpses. His skill and renown were enough to secure his being named as the professor of botany at the Athenaeum Illustre in 1666. His pathway to success continued with being named the chief instructor to midwives in 1668 and forensic advisor to Amsterdam's courts in 1679.

Ruysch made many significant scientific contributions to anatomy in particular, because of the freedom he was allowed as the praelector. He described the valves in lymphatics and wrote a paper on the vomeronasal organs of snakes. Frederik also demonstrated the bronchial circulation and the first good case description of rectal carcinoma. He became particularly interested in the preservation of anatomical specimens and developed a secret *liquor balsamicum* that could keep specially prepared anatomical curiosities lifelike, in order to demonstrate to students. He used a combination of wax, resin, talcum, oil of lavender, cinnabar, and colored pigments to both preserve his specimens and overcome the offensive odor of necrosis. In June of 1666 English admiral William Berkeley was killed in a battle with the Dutch fleet. Ruysch was called upon to preserve the body in the height of summer, an almost impossible task prior to his injection of preservatives. But the British compensated Ruysch for his amazing anatomical preservation of Berkeley [10]. As praelector of anatomy for the surgical guild, Ruysch utilized his skills in both dissection and preservation of specimens in public demonstrations of anatomy. As a result, his collection of anatomical specimens began to attract increasing attention to his demonstrations. Ruysch began to take a more artistic interest in his specimen presentation, and the collection increased in fame [11]. He was mandated by the guild to perform at least one anatomical dissection annually open to the public. By 1670, Ruysch had achieved significant renown that the Amsterdam surgeon's guild had the famed artist Adriaen Backer paint him in an "*Anatomy Lesson*" much as Rembrandt had done for Dr. Tulp, another anatomist from the guild (Fig. 14.3a). Ruysch though would go one better, sitting again in 1683 for a second anatomical portrait, this one by Jan van Neck (Fig. 14.3b) [12].

Ruysch's success allowed him to involve his family into his business. His son, Frederik, became an able anatomical demonstrator and would in turn become a physician. His daughter, Rachel, became an illustrator and collaborator upon the artistic nature of his menagerie and she became a famous painter [13]. Rachel in fact might have been the child who is holding the skeleton in the 1683 van Neck painting. She certainly helped create his artistic renditions of anatomical specimens. She became a still life

Fig. 14.3 (**a**) This is the first commissioned painting of Ruysch by the Surgeon's Guild in 1670 (Backer), Amsterdam's Historisch Museum. (**b**) This is the second commissioned painting of Ruysch by the Surgeon's Guild in 1683 (van Neck). His son (Frederik would have been aged 20 at this time) is shown demonstrating a fetal skeleton (or is it his daughter, Rachel?)

painter of outstanding merit in her own right; her paintings would become worth more money than Rembrandt's in their lifetime [13]. Frederik had become Holland's premier anatomist and dissector. He is known to have given at least 31 public dissections, continuing up until his death at age 92. He was also known as a surgeon and obstetrician. His interests are clearly reflected in his anatomical demonstrations. He was much interested in the kidney and dissected it and illustrated the anatomy in several of his written works. The anatomical theater in Amsterdam became Ruysch's own "*Rariteiten-kabinetten*" or "cabinet of rarities or curiosities" [11]. He often worked alone with his son and daughter improving his secret preservative by minimizing the odor of the dead, improving the water retention of the specimens so that they did not look shriveled, and added color to make them more spectacular [14]. His published catalogue in 1691 entitled "*Frederici Ruyschii Thesaurus Anatomicus*" or *anatomical treasures* was lavishly illustrated by famed artist C.H. Huyberts. He brought these volumes out between 1638–1731 in ten volumes. Ruysch by this time had begun to add human kidney stones to his animations in order to improve their artistic presentation [8]. Many of the collections animated classical poetry; in all he made more than a dozen tableaux utilizing human kidney and gallstones. Some of his poetic renditions included *Vita humana lusus* (Man's life is but a game) and *Vita quid est*? *Fumus fugiens et bulla caduca* (What is life? A transient smoke and a fragile bubble). Frederik Ruysch became an intriguing historical figure, worthy of some attention at kidney stone meetings, precisely because he chose these concretions to serve as one of the "finishing elements" in several of his collections [4].

Ruysch's Use of Kidney Stones: Exhibits

Ruysch eventually began to use prosected animal specimens in jars of preservative as even more elaborate displays [14–16]. His most morbidly fascinating exhibits had fetuses dressed in a variety of costumes. Frederik Ruysch combined his skills as a dissector with an obvious natural artistic talent to make some of the most unusual anatomical displays, often utilizing a growing collection of human stone material. He would sift through his collection of calculi in order to obtain particular shapes that added to the scene he had imagined [4]. The haunting character of the C.H. Huyberts drawings are sadly all that remain of these curiosities. He found a purposeful use for stones extracted from patients in Amsterdam as scenery for his whimsical renderings. By 1697, the fame of his collection had reached Peter the Great who came to visit him and his collection. His "*repository of curiosities*" included infant and fetal skeletons placed in landscapes accented by human pathology and animal body parts. Human kidney stones were a common decorative item in these displays. Ruysch spent hours meticulously preparing his specimens for presentation. He involved the artistic talents of his daughter, Rachel. He wrote to Boerhaave in 1722 "*Never does that sun rise too early for me, and nightfall always comes sooner than I could wish*" [16]. Ruysch became fascinated with the anatomical museums while a student at Leiden. Ruysch represents the epitome of the Dutch Golden Age of Anatomy. The Flemish nobleman Lodewijk de Bils first hit upon a formula for preservation of human organs. He utilized a liquor which bathed the specimens, and he also injected the vessels with waxlike colored materials to enhance the image [10]. These preserved specimens could be viewed repeatedly and did not rapidly decay. The Leiden anatomical theater was a literal museum of such displays and these fascinated young Ruysch who developed his own secret method of preservation.

Some of the most dramatic illustrations utilizing human stones for effect were his moralizing vanitas. A vanitas was a type of symbolic art form that became a fad in both Flanders and the Netherlands [17]. It derives from the Latin root meaning vanity. Death was a common subject as was the transient nature of life and skulls were particularly popular adornments to this type of art. The stones would give the vanitas a sense of naturalism. The two most famous stone relief vanitas were both illustrated in his third *Thesaurus Anatomicus* of which there are no surviving originals. The first is *The Allegory of Death* (Fig. 14.3a). The central skeleton has an osteomyelitic sequester and a dried artery for a violin to play a lament for life's miseries [18]. The meter of the music is kept by a skeleton with a baton set with kidney stones (center right). On the far right is a skeleton holding a spear made from vas deferens and coils of sheep's intestines. The feathered skeleton on the far left holds a stone from the lung and is standing next to a fixed human testicle complete with all of its tunics. In the foreground is a reclining skeleton holding the evanescent mayfly which completes this depiction of the brevity of life. He particularly liked to use fetal skeletons because it highlighted the uncomfortableness of the topic he chose to represent. He would use mottos for these vanitas typically taken from Latin poets like "*Vita quid est? Fumus fugiens et bulla caduca- What is life? A transient smoke and a fragile bubble*" [4] (Fig. 14.3b).

Ruysch did train the German physician and anatomist Bernhard Siegfried Weiss (1697–1770) (Latinized to Albinus) who would later become the great anatomist at Leiden. Albinus also worked with his great rival Bidloo and also with Rau. It appears that Albinus never joined into the anatomical disputes with his former anatomical mentor from Amsterdam. Albinus also developed his own methods of preservation and injection and much of his work survives at the Boerhaave Anatomical Museum at Leiden [19]. He also became famous as the person who tried to teach Cheselden Rau's technique of the lateral lithotomy, but Rau had secretly hidden key portions of the surgery from his pupil Albinus as well. Cheselden was forced into investigating the anatomy and surgical approaches for the lateral lithotomy on his own and subsequently taught this approach to all who were interested in this surgery [20].

Peter the Great

Peter the Great (1672–1725) was born on May 30, 1672, the son of Tsar Alexis and his second wife Natalya Naryshkina [21]. He was a vigorous individual and has been described as a "*chimerical monarch*." In 1697 he embarked upon "*The Great Embassy*" to learn about the western world when he was only 25 years old. For eighteen months he and his entourage of 20 nobleman and 25 young Russian volunteers dispersed throughout Europe to learn about the West and particularly the art of shipbuilding and warships themselves. He was incognito as Peter Mikhailov so that he personally could visit shipyards and discuss nautical science with the carpenters and builders. He became particularly enthralled with Holland which was at its zenith culturally. In Amsterdam, Peter actually worked as a carpenter himself in the dockyards of the Dutch East India

Company. Peter was greatly interested in medicine and science. He is known to have traveled to Delft to visit with Anton van Leeuwenhoek (1632–1723). He also went to Leiden to visit Boerhaave. But singularly the most important interaction for the young emperor was his interactions with Frederik Ruysch. "*This great figure of world anatomy impressed the emperor and inspired his love for anatomy and surgery*" [22].

Peter and Dr. Ruysch clearly interacted more significantly than any other individual during his *Great Embassy*. "*Several times, Peter left the shipyard to visit the lecture hall and dissecting room of Professor Ruysch, the renowned professor of anatomy. Ruysch was famous throughout Europe for his ability to preserve parts of the human body and even whole corpses by injection of chemicals. His magnificent laboratory was considered one of the marvels of Holland…Peter became so interested in surgery that he had difficulty leaving the laboratory; he wanted to stay and observe more. He dined with Ruysch, who advised him on his choice of surgeons to take back to Russia for service in his army and fleet. He was intrigued by anatomy and thereafter considered himself qualified as a surgeon. After all, he was able to ask, how many others in Russia had studied with the famous Ruysch?*" [21]. The emperor would not forget his anatomy teacher or the master's anatomical museum, as we shall see.

In 1717 Peter the Great returned to Amsterdam and purchased Ruysch's museum for the astronomical sum of 30,000 guilders putting Ruysch and his family in the wealthiest class in Amsterdam during its Golden Age. In addition, he purchased Ruysch's secret preservation techniques for an additional 5,000 guilders [22]. This was quite the coup for the aging anatomist. But he went right back to work on another series of specimens and anatomical preparations; he was only 79 years old. Ruysch's nemesis and sparring partner in pamphlets regarding anatomical battles was Govard Bidloo (1649–1713) [23]. Bidloo had died vacating his anatomy chair at Leiden for the rising lithotomist, Johannes Rau. Bidloo's famous anatomical museum fetched at auction barely 177 guilders. His library fared far better raising about 3,000 guilders for his widow Hendrickje Dircksz [10]. In addition, the publisher of his magnum opus *Anatomia humani* corporis published in 1685 sold the beautiful illustrative plates to the anatomical instructor of William Cheselden, Cowper who utilized them in his own textbook of anatomy without any deference to Bidloo [10].

Anatomical Controversy and Surgical Upheaval

Ruysch was a firm believer that his anatomical preparations were lessons in anatomy of themselves. He strove to create the illusion of life with his wet preparations, injecting color to create the illusion that his specimens were fresh and lifelike. The anatomists at Leiden were apposed to this realism, let alone the surrealism that some of tableaux engendered. "*The study of medical museums, then, sits at the historical confluence of some very interesting streams of thought- medicine, collecting, the body- which then flow into contemporary debates about display and use of human remains*" [2]. His successes anatomically were not allowed without some attacks by those who could not duplicate his delicate preparations. Most notably was the gifted anatomist Govard Bidloo. For almost one decade during most of the 1690s, these two highly skilled anatomists dueled with one another over the best methods of presenting and teaching anatomy. The maliciousness of these attacks is notable from the pains that Bidloo went to count how often Ruysch used the word "*mirum*" and its cognates in his work *Epistolae* and *Observationum centuriae* (Bidloo counted 96 times) [10]. Bidloo spent most of his time creating his surgical atlas with superior illustrations on paper for his book [24]. Ruysch, on the other hand, spent all of his time making anatomical preparations and criticizing the work of Bidloo the flaws of illustration. In the end Bidloo's *Anatomia humani corporis* did not sell well and the publisher ended up selling his anatomical plates to William Cowper (1666–1709) who unjustly did not credit Bidloo's work when he published his far more popular work, *The Anatomy of Humane Bodies* in 1698 (13 years after Bidloo's work was printed) [25].

We will discuss in the surgical historical section regarding lithotomist Jacques Beaulieu (1651–1714) who was an unheralded military surgeon who developed a novel method of performing the ancient operation of perineal lithotomy [26]. He daringly came to Paris to demonstrate his new method of lithotomy and gained both powerful allies and enemies. Eventually he was driven out of the surgical capital of the world by Marechal who was one of the best lithotomists in Paris. He traveled to the lowlands of the north, and the King of Holland sponsored his entrance for demonstrating his new surgical methods. He appears to have been welcomed by Frederik Ruysch, and all of the Amsterdam surgeons came to watch his method of lithotomy. Johann Jacob Rau was a struggling surgeon in Amsterdam at the time who watched and knew that he could improve the method due to his extensive knowledge of anatomy. There was considerable tension between Ruysch and Rau that would continue for the remainder of Rau's life; in fact he would become Ruysch's major antagonist when Bidloo moved to England. Rau would be invited to Leiden to become Bidloo's successor as professor of anatomy. Rau adopted Beaulieu's method of lithotomy and became the most successful lithotomist in all of Holland at the same time becoming the most vociferous detractor of Jacque's methods. Frère Jacques was recalled to Paris by his friends but again things did not go well and he returned to Amsterdam in 1704. "*Rau, whose rare talents and incomparable meanness of disposition kept an almost equal pace, so that we know not whether most to admire or detest the man, published like Mery, his daily scandals, dissected Frère Jacques out of the capital, yet stole the very operation which he affected to condemn*" [27]. Rau was clearly responsible for his early departure during this second sojourn and he traveled on to Brussels [28]. The Dutch senate gave Jacques a medal with the inscription "*Ob cives servatos,*" and he was encouraged to return again, which was never again to happen. He did write to his friends in Amsterdam, "*Why should I return when you have already a man so much above me as Rau?*" [29] It has been estimated that Jacques removed over 4,500 stones with surgery and that Rau performed possibly 1,500 as well. It had been estimated that bladder stone disease had the highest prevalence in the Netherlands accounting for Ruysch's ready access to them for his vanitas. It was van Beverwijck who was the first to note the high prevalence rate of stone disease in the Low Countries in 1638 [29].

We know little about Frère Jacques' interactions with Ruysch. Ruysch certainly did not get along with Rau but there is mysterious silence about this potential situation. Even de Vries noted "*Professor Joh. Jacques Rau a lithotomist and bitter rival, who pursued Frère Jacques with such a fierce criticism that he decided to leave Amsterdam. Rau's behaviour was not without self-interest since he used the lateral method of lithotomy extensively after a few adaptations for the rest of his active life in Leyden*" [29]. Jacques only said negative things about Rau and never mentioned Frederik Ruysch. That Rau could not be trusted was certainly the case, for he always hid his methods from even his most trusted pupil and heir, Albinus. Albinus who was asked to write the memorial dissertation regarding Rau was never shown by his mentor the secret of his successful lithotomy technique—this had to be worked out independently by Cheselden on England [30]. In this funeral oration by Albinus, he states that Rau claimed to have operated upon 1547 bladder stones during his career. The specific cause of Rau's great secrecy was his greed for money; it has been noted that he charged "*200 Rijksdaalder for students and visiting colleagues to enroll in his teaching program. This amounted to an average year's salary of a master surgeon in a smaller town*" [29]. In addition, Rau was not above charging as much as 1000 or more florins for a successful operation [29].

Discussion

"*All movables of wonder, from all parts,*
Are here- Albinos, painted Indians, Dwarfs,
The Horse of knowledge, and the learned Pig.
The Stone-eater, the man that swallows fire,

Giants, Ventriloquists, the Invisible Girl,
The Bust that speaks and moves its goggling eyes,
The Wax-work, Clock-work, all the marvelous craft
Of modern Merlins, Wild Beasts, Puppet-shows,
All out-o'-the-way, far-fetched, perverted things.
All freaks of nature, all Promethean thoughts
Of man, his dullness, madness, and their feats
All jumbled up together, to compose
A Parliament of Monsters." [31]

William Wordsworth's autobiographical poem that conjured up the macabre image of the Parliament of Monsters became the introductory chapter to a textbook on the history of pathology museums. Wordsworth was commenting on the bizarre spectacle that he observed attending the Bartholomew Fair in Smithfield, London [32]. This could be easily applied to the anatomical theaters that had arisen with the rise of human dissection. At Padua, Benedetti's creation of the first anatomical theater built in 1594 led to a permanent structure that was carefully constructed for almost theatrical production [33]. The great professor of anatomy Fabricius dissected in front of 200–300 spectators carefully arrayed in concentric galleries around the central anatomy table which could be raised into the theater. Great anatomical theaters were constructed at Padua, Bologna, Leiden, and Monkwell Street in London for the barber-surgeons in 1636. Anatomists were increasingly fascinated by the average person's enthrallment with the morbid subject of anatomy. At some point, the anatomists realized that they could translate this spectacle of anatomical dissection into a more durable art form. That is what Frederik Ruysch really vaulted into the stratosphere of public acclaim. His anatomies and allegorical themes were aided by his deft use of human concretions to form visual art, aided of course by his daughter Rachel.

"*In old-fashioned museums you can see the unconscious benefactors of mankind, trapped in glass cases: the freaks and monsters of their day, the anomalies, sometimes skeletonised and entire, sometimes cut into parts and labeled. When we look at them, fascination and repulsion uneasily mixed, we bow our heads to their contribution to knowledge, but it is hard to locate their humanity. The thread of empathy has frayed and snapped. They have become objects, more stone than flesh: petrified, post-human*" [34]. Ruysch eventually developed a relationship with Herman Boerhaave at Leiden and continued to do public anatomical demonstrations throughout his very long life. He and Boerhaave developed cordial discussion and significant differences regarding glandular function. Ruysch's fame led to his election to the Leopoldine Imperial Academy in 1705. He became a fellow in the Royal Society of London in 1720 and was chosen to take the vacated seat of Sir Isaac Newton as an associé étranger to the Académie des Sciences in 1727 [4]. Yet Ruysch's fame rested upon his museum and its unusually artistic representations of human anatomy [16]. Lorenz Heister who knew Boerhaave, Rau, Albinus, and Ruysch when he became the professor of surgery and anatomy in Helmstedt stated that Ruysch was the one who contributed most to the growth of anatomical knowledge in 1720.

Ruysch in many ways represents the most extreme showcase for urinary stone disease with his innovative decorative applications within his menagerie. Certainly the Roman Catholic Church had presented relics of saints and upper echelon priests, bishops, cardinals, and popes for centuries. These were mostly bones but occasionally were mummified remains which we'll see again in a later chapter. Wax models were utilized prior to the anatomist development of preservatives and methods of display [35]. Anatomically, he precedes the current anatomical art of Gunther von Hagens' Body Worlds which has been viewed by over 20 million visitors worldwide between 1996 and 2006 [36]. "*Small minds have usually viewed Science and Art as adversarial- at least from Goethe's complaints about narrow-minded naturalists who would not take his anatomical and geological works seriously because he maintained a day job as a poet to C.P. Snow's identification and lament about two non-communicating cultures…But the unifying modes and themes of human creativity surely transcend the admitted differences of subject matter in these two realms of greatest interest and occasional (even frequent) triumph of both heart and mind*" [37]. "*Mortui vivos docebunt* or *the dead shall teach the living*" is the famous motto on many of anatomical laboratories around the world [38].

Two significant giants of anatomical preparation followed in the wake of Ruysch and Albinus: they were Honoré Fragonard (1732–1799) and John Hunter (1728–1799). Both were outstanding anatomists who spent a considerable amount of labor and effort into anatomical teaching and preparation of specimens for display. Fragonard's preparations might be considered the origins of Gunther von Hagens' own modern traveling shows of anatomically plasticized human works. Ruysch utilized human concretions as backdrops in his vanitas but von Hagens' has utilized all modern medias mixing Goethe's contrasting roles even further into realms of religious, philosophical, and even prophetic views of man and nature [39].

Herman Boerhaave (1668–1738) evolved into one of the most important figures in eighteenth-century medicine. He also suffered from gout and urolithiasis later in his life, but he foreshadowed his own suffering, much as Benjamin Franklin did, with his writings on disease, specifically on urolithiasis. He had a ringside seat for the controversies regarding lithotomy and personally saw the rise and successes of the lateral lithotomy developed by Rau using the method of Frère Jacques. It was during this century that the rise of anatomy and surgery began to tabulate and reduce the morbidity and mortality of surgery, but anesthesia and aseptic methods had not yet been introduced. Boerhaave dedicated a chapter in his "*Institutiones medicae*" to the treatment of lithiasis of the urinary tract [40]. His recommendations included an increase in liquid intake, a hot bath in order to induce vasodilation, and exercise. Boerhaave's opinion of lithotomy as a last resort when other approaches failed was "*I think lithotomy is an act of pure faith*" [41].

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15 Gray's Anatomy of Stones: Henry Vandyke Carter

Introduction

The history of anatomy is vital up until the nineteenth century and its relationship to stone disease is the subject of this chapter. We just spent one chapter looking at the use of a common pathologic material, urinary calculi in the morbid anatomy, or anatomical art with Frederik Ruysch serving as the inspiration. Now it is time to turn our attention to the development of our understanding anatomy and how this relates to stone disease. This will require a bit of background as the history of anatomy is complex and represents a huge segment of historical medical research. We will consider a singular moment in the nineteenth century when a gifted duo of physicians decided to create a manuscript to aid in the learning of anatomy. One would continue his brilliant career and publish a work on urolithiasis and the other would die tragically young of confluent smallpox. The other would live a long life and contribute significantly to medical knowledge, while his name was virtually erased by his colleague as the myth of Gray's Anatomy propagated. Following in the wake of this little heralded anatomist were others, and the Hunterian collection itself will be the final consideration during this chapter.

But anatomy does not have to be a dried, morbid business. Some anatomists, surgeons, and stone sufferers have made the renal anatomy come alive by their rhapsodizing over the urinary tract. Richard Seltzer is a surgeon, writer, and stone sufferer: "*Delicate durability describes the human body, and nowhere is this more apparent than in the urinary tract. If the liver is all bulk and thunder, the heart fist and thrust and piston, and the brain a foamy paste of insubstantial electricity, the parts of the urinary tract- are a tracery of tubules and ducts of such a fineness as would lay mad a master plumber, more, a Venetian glassblower…The ureters, a foot or more in length, are drawn out the finest filaments before joining the bowl of the bladder. This virtuoso fills passively, until, aroused by its own tidal volume, its contracts in vigorous expression. From its nethermost surface, the tapered spout of the urethra extends to deliver to the out-of-doors the jet of urine that is the raison d'être of the whole mechanism*" [1].

Anatomy Lessons

In order to understand an illness, it is first essential to understand health. The study of anatomy must therefore make the physician aware of what is normal [2]. This argument is also old; Morgagni in the preface of his towering 1761 treatise *De sedibus et causis morborum* which we discussed briefly in the Enlightenment chapter criticized his predecessor Théophile Bonet of Neuchâtel (1620–1689) on the first real treatise of pathologic anatomy *Sepulchretum: sive antomia practica ex cadeveribus morbo denalis* in 1679 [3]. Here he stated that it was inaccurate and misleading, proceeding from ignorance of normal anatomy that

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introduced error into Bonet's pathology [4]. Anatomy is the foundation of the science and art of medicine. In a recent historical overview, Prof. Franz Marx has used the earliest surviving Greek and Roman manuscripts to clarify the anatomical history [5]. He credits Alcmaeon of Croton to have performed the first animal anatomies and possible vivisection between 570 and 500 BCE. The Hippocratic physicians between 430 and 350 BCE used only sporadic and unsystematic dissections on animals to augment their knowledge of the body. Aristotle without question dissected animals and performed vivisection between 384 and 322 BCE. Herophilus of Chalcedon was a student of Praxagoras of Cos and was attracted to the Hellenistic epicenter, Alexandria, under the rule of the great general Ptolemy I who ruled Egypt following the death of Alexander the Great. Between 330 and 250 BCE, he performed anatomical dissections and probably vivisections of human beings, most likely criminals [6]. Herophilus wrote at least eight books about his findings; sadly none of these remain and only secondary sources (Galen, Rufus of Ephesus, Celsus, and Soranus of Ephesus) [5]. Erasistratus followed Herophilus and is considered to be the father of physiology. The fall of human dissection might be directly linked to Herophilus' pupil, Philinus of Cos, who became the proponent of the empiricists who rejected anatomy and dissection in the third century BCE. The legacy of these two founders of anatomy laid the basis of anatomical structure. It is Galen's volumetric writings that give some legacy to Herophilus and Erasistratus' discoveries. Herophilus gave us a detailed description of the liver, gall bladder, bile ducts, pancreas, and duodenum and compared the male and female reproductive systems. They realized that the pulsations of the arteries came from the heart and that breathing was from the thorax and the lung, not the heart. Galen performed animal dissections, vivisections, and experimentation but really was enshrined by his volumes of written works between 129 and 210 CE [7]. Galen rejected the notion of Aristotle that the kidneys functioned to separate surplus liquid from the blood and to make urine. Galen rejected the sieve-like action of the kidneys but thought they attracted the urine from the blood. Oribasius who lived from 325 to 395 CE, Aëtius of Amida in the sixth century, and Paul of Aegina in the seventh century CE all contributed bits and pieces to anatomical knowledge. Paul would add the perineal lithotomy anatomy that was discussed by the Roman encyclopedic author Cornelius Celsus in the first century CE [5].

Table 15.1 Famous anatomists at Padua

Pre-Vesalian: Benedetti (1455–1525)
Andreas Vesalius (*1514–1564*)
Post-Vesalian: 1. Realdo Colombo (1516–1559) 2. Gabriele Falloppio (Fallopius, 1523–1562) 3. Girolamo Fabrizio d'Acquapendente (Fabricius, 1533–1619) 4. Giulio Cessario (Casserius, 1552–1616) 5. Adriaan van den Spieghel (Spigelius, 1578–1625)

Andreas Vesalius is credited as the founder of modern medical anatomy, reawakening critical thinking and investigation with the publication of his monumental *De humani corporis fabrica libri septem* from Basel in 1543 [8]. The doors of knowledge were flung open, the sanctity of Galen was in doubt, and the rise of anatomists interested in extending mankind's understanding of the body did not have to wait long for further answers. The list of professors of anatomy just at the University of Padua where Vesalius taught reads like a modern Who's Who (Table 15.1). Matteo Realdo Colombo (Columbus, 1516–1559) was also the son of an apothecary, like Vesalius, but studied at the University of Padua and became the anatomist's assistant [9]. While Vesalius was on leave to publish his *Fabrica* in 1542, Colombo assumed his duties as lecturer in anatomy. He assumed temporary chair of anatomy in 1543 and was paid 80 florins per year until Vesalius returned. In the first edition of *Fabrica,* Vesalius referred to his assistant as "*my friend Colombo, skilled professor at Padua, most studious of anatomy*" [9]. For some presumed slight he removed Colombo from the second edition, and in the 1546 *Letter on the China* Root he now calls Colombo "*…who learned something of anatomy by assisting me in my work, although he was* *incompletely educated; several times he had heard in the medical school that I was unable to find a passage or vein- actually a fiction of most anatomists- and while I was absent from Padua he dissected a body and boasted that he found something that was unknown to me*" [9]. Colombo would go on to note correctly that the right kidney was in fact lower than the left and corrected Vesalius' error by relating that there are no septa between the ventricles. He was lured from Padua by the Medici's to Pisa and eventually was appointed professor at Sapienza in Rome in 1548. He treated Ignatius Loyola for kidney stones and performed his autopsy. He reported the pathologic findings in the last chapter of his *De Re Anatomica:* "*With these my hands have extracted numerous calculi of various colors found in the kidnies, in the lungs, in the liver, in the portal vein, as you Jacopo Boni have seen with your own eyes, n the Venerable Ignatius, founder of the Congregation of Jesus, in whom I saw the stones in the ureters, in the bladder…*" [9] Colombo would become the physician who would treat Michelangelo's stone disease. Vasari notes "*…in his old age he* [Michelangelo] *suffered from gravel in his urine which finally turned into kidney stones, and for many years he was in the hands of Master Realdo Colombo, his very close friend, who treated him with injections and looked after him carefully*" [10].

Contemporary to Vesalius was Bartolomeo Eustachio (Eustachius c.1510–1574) who was a physician and anatomist in Rome. Eustachius came from a family of physicians and began his life as a classics scholar. He studied medicine at the Archiginnasio della Sapienza in Rome (where Malpighi would end his career) and began to practice by 1540 [11]. He did many dissections and used the artistic talents of Pier Matteo Pini to make 47 copper-engraved plates for his planned anatomical treatise. In the 1560 s he did publish a treatise on the kidneys, *De rerum structura* which was the first work dedicated to this organ with eight plates. The remainder of his work simply vanished after his death but was published again with the missing 39 plates by Lascisi in 1714 with the help of Morgagni [12].

William Harvey (1578–1657) was obsessed with experimental anatomy and physiology, a graduate of the University of Padua and substantially influenced by Fallopius (successor to Colombo). He wrote his magnum opus in 1628 (*De motu cordis et sanguinis in animalibus cordis*) and also suffered from bladder stones [7]. Nicolaus Steno (1631–1686) was a Danish anatomist and physician who did work in Paris where he discovered his eponymous duct of the parotid glands. He then matriculated to Padua where he became a professor of anatomy in 1666. He left for Florence where his academic output was significant [13]. He suffered from recurrent bouts of colic and kidney stones prior to becoming a Roman Catholic priest. Anatomy began to spread to new centers of excellence, at Leiden and Edinburgh.

Marcello Malpighi (1628–1694) kept the Italian tradition alive at the University of Bologna. Malpighi was a child prodigy; he received his diploma from Bologna at the age of 17 with reverendissimus dominus (honored master) [14]. Malpighi's brilliance included pushing the envelope of experimental anatomy by introducing the microscope in his studies. Many eponyms in anatomy are directly attributed to him including the Malpighian tubules and the renal pyramids [15]. Ferdinand II, the Grand Duke of Tuscany, offered this gifted anatomist the chair of theoretical medicine at the University of Pisa which he accepted for three years where he influenced a brilliant pupil, Giovanni Alfonso Borelli (1608–1679). Borelli went on to publish his *De motu animalium* in 1680 where he discussed the mechanical abilities of the organs of animals, including the kidneys. His proposition CXL states "Urine is separated from the blood in the kidneys mechanically as a result of the narrowness and configuration of the vessels" [16]. His sieve-like mechanism is different from that of Aristotle's and is more a function of the vessels, akin to that proposed by van Beverwijck. Another Italian physician/anatomist was Lorenzo Bellini (1643–1704) who published his *Exercitatio Anatomica de Structura et Usu Renum* in 1662 [17]. Bellini proposed that the serum is separated from the blood and is secreted into hollow tubules that enter the renal pelvis, called ducts of Bellini. Malpighi published his monumental *De Viscerum Structura Exercitatio Anatomica* just three years later demonstrating that the kidney was not solid but an organized structure of "glandular units" which in the renal cortex formed urine. These glands became known as Malpighian corpuscles. Malpighi made many brilliant observations and was a lightning rod for controversy between the "old guard" physicians and the new theoreticians [18]. He corresponded widely with the Royal Society and maintained contact with Borelli and the literati in Paris. It is ironic that Malpighi probably also suffered from kidney disease and died on July 25, 1694 [18].

Malpighi was also the consummate clinician [19]. His monumental achievements in anatomy, physiology, and embryology brought him significant acclaim, but his clinical practice likewise flourished. Malpighi maintained a large consultative medical practice throughout his career. As his fame grew, so did his practice. He absorbed all of the medical knowledge and maintained a wide correspondence [19]. He read and approved of both Thomas Willis's work from England and the gifted medical anatomist Nicolaus Steno. He was a proponent of the "real Hippocratic medicine" not the Arabic version of this. For stone disease he would prescribe mild herbals. If not relieved he would proceed with chalybeates (solutions of iron or steel), perspirants to favor sweating (from Steno), and bloodletting. He never wrote specific medical texts; however he often in his consultations talked about healing, derived from his knowledge of disease obtained via his research. It was from Malpighi's medical practice that he made connections among anatomy, pathology, and therapeutic efforts that make him seem so modern. In his *consulti*, written documents of consultation, there have been over 217 published; he would rarely pass up the opportunity to explain the disease using the new language of chemistry and mechanics [19]. This new concern for the science of medicine is disclosed in his praise for another physician/scientist Francesco Redi: "*He found time to practice medicine, to engage in political matters without neglecting his domestic concerns, and to conduct investigations into natural things with praise and honor*" [19]. Despite these laudable standards, he still fell into the trap of importing specially concocted human blood therapies from Robert Boyle to try on his patients (see section on Quacks).

Giovanni Battista Morgagni (1682–1771) continued the tradition of outstanding anatomists at the University of Padua. He matriculated at the age of 16 to Bologna and graduated in 1701 and became the prosector to his mentor, Antonio Maria Valsalva (1666–1723) [20]. Valsalva was a student of Malpighi's and also was a proponent of microscopic anatomical work that somehow never took with Morgagni. Morgagni was attracted to Padua in the spring of 1712 at age 35 and assumed the chair of anatomy three years later which he held until his death in 1771 (59 years). In 1761 he published *De sedibus et causis morborum* which records his observations for over 50 years of diseases with detailed autopsy findings, relating symptoms, and illness to pathology. He wrote *De sedibus* in the form of letters to a young friend [20]. There were seventy letters, arranged in the now archaic fashion based upon symptoms. The letters were divided into five books that total an astounding 646 dissections. He included many cases of stone disease in his pathology, including the first documented case of foreign body encrustation resulting in the death of this fourteen-year-old girl. Morgagni believed that all stones started in the kidneys: "*Now it frequently happens that small stones are held in these membranous ducts and are enlarged by the accretion of tartar, so that they injure the delicate membrane of the vessels and consequently the flesh of the kidneys is often observed to be destroyed*" [3].

Frederik Ruysch (1638–1731) in 1701 published *Theatrum Anatomicaum* which shows the capillary tufts that would be the glomeruli. He discussed it in detail previously. His pupil, Govard Bidloo (1649–1713), also became the subject of his ire like Vesalius and Colombo [21]. Bidloo was antagonistic to his mentor's artistic interpretations of death and cadavers; he strove to enshrine the "martyrs" and suffering of the deceased in his position as professor of anatomy at The Hague in 1688 [22]. By 1694, Bidloo succeeded Anton Nuck as professor of anatomy and surgery at the University of Leiden. Ruysch continued in the line of great anatomists to publish a series of booklets that criticized his former pupil's work. William Cowper (1666–1709) published his *The Anatomy of the Humane Bodies* in 1698 and was elected into the Royal Society in 1696. Cowper took tremendous liberties utilizing the work of Govard Bidloo's (1649–1713) *Anatomia Humani Corporis* from Amsterdam in 1685 which included 105 plates. But since sales were poor, the publishers sold 300 copies to William Cowper or his publisher. Cowper did write new text for his book and made some original research. In addition, he had nine new plates made by Henry Cooke. Cowper however made no mention of Bidloo or his book in his textbook [22]. Sir Hans Sloane, the secretary to the Royal Society and a collector of unusual stones that later would join the collection of Hunter's, had to write an uncomfortable explanation to Bidloo explaining the Royal Society's role in Cowper's publication, "*that the Society are not erected for determining controversies, but promoting naturall and experimentall knowledge, which they will do in him or anybody else*" [23].

Cowper's most famous pupil was William Cheselden (1688–1752) who wrote his treatise on anatomy in 1713 *The Anatomy of the Human Body*. This work included 40 leaves of anatomical plates that went through 16 English and American editions through 1806 [24]. Cheselden adopted Frere Jacques's lateral method of perineal lithotomy and became famous throughout the world as a lithotomist. In addition, his most famous pupil was John Hunter (1728–1793) who is considered the father of scientific surgery and surgical research. Hunter was clearly fascinated with stone disease [25]. He recorded that renal calculi occur more commonly in animals than in man, which he attributed to the horizontal posture. He hypothesized that the position of the animal's kidneys was such that it obstructed drainage of urine from the kidney to the bladder which was corrected by the upright posture of man. In addition, Hunter after studying teeth speculated that the crystallization of substances in solution, such as urine, led directly to the formation of stones. He compared stones of many animals and collected an enormous quantity of these concretions which were first categorized and presented by his student Richard Owen in 1861 [26]. Hunter was clinically active as well as performing research. In his casebook from November 1757, he reports on an autopsy of a man who died with kidney stones:

> November 1757
> *'A man was dissected, and on Examining the Kidneys, we found that on the left side was diseased. Its sise was rather less than the other, The Fat Surrounding that was hard, and adhered very firmly to it. When this was removed I found the Surface of the Kidney very irregular and White, especially at the risings, and on cutting into those white Nobs there came out a thick white mucous like white paint, or chalk and water mix't.*
>
> *'I examined the Pelvis, and found a Stone of a black colour and the rest of the pelvis fill'd w' white Substance.*
>
> *'I divided the Kidney nearly into two. It's substance was very firm and white. If found three or four Cists filled with white matter, and one of the Cists had its coat Ossified, and contained clear water In one of the Cists that contained the white matter, was a Stone like that in the Pelvis, but no biger than a Pea- the Cistes seemed to be in the Corticle substance than in the tubul: Vide diseased Kidneys No. 2.'* [26]

Alexander Schumlansky (1748–1795) was a Russian physician who studied at Strasbourg till 1783. His inaugural dissertation *De Structura renum* (1782) was a 138-page work with two illustrations on the structure of the kidney, reviewing all ancient and current information on the kidneys [3]. Friedrich Gustav Jakob Henle (1809–1885) studied medicine in Bonn and Heidelberg and began to use his microscope to study the kidney's tubules. In 1862 he discovered the epithelial nature of the convoluted and straight portion of the cortical tubules and the medullary and papillary collecting tubules (described by Eustachius and Bellini). He noted two types of tubules in the medullary portion of the kidney. The papillary collecting duct was lined with a uniform epithelium in which the height of the cells increases near the papillary tip. The second type was much smaller and is lined by small squamous cells. Henle noted that these smaller tubules ran parallel to the collecting ducts but return in a narrow hairpin loop into the medullary tissue and that these are arranged in a circular fashion around the collecting ducts [27]. William Bowman (1816–1892), a demonstrator in anatomy at King's College, London, and elected a fellow in the Royal Society at age 25, used a microscope and vascular injection to describe the relationship of the glomerular capillary tuft to the afferent and efferent arterioles. He also described how the vessels break up into a second capillary plexus closely applied to the basement membrane of the tubules [28]. Bartolomeo Camillo Golgi (1843–1926) is best known for his work on neuroanatomy and his contentious interactions with his fellow neuroanatomist, Santiago Ramón y Cajal. They historically clashed following their shared Nobel Prize in 1906 [29]. Golgi made many contributions; however, it was his contributions to our understanding of renal anatomy that calls for our attention. In 1882, Golgi published his first paper where he discloses the mechanism of compensatory hypertrophy of the kidney was due to tubular proliferation. He followed these pioneering studies with observations on acute renal injury in patients with Bright's disease in 1884. In 1889 he made his most important contribution to our understanding of renal tubular anatomy. He noted that embryo logically from what part of the S-shaped metanephric structure the various tubular segments originate. Golgi developed a new technique for studying whole intact nephrons. Utilizing his method he was able to demonstrate that the ascending loop of Henle returns to the glomerulus from which the tubule originated, using the words *con legge invariable*, with invariable law [30]. The anatomy of the kidney was now almost up to current standards.

Gray's Anatomy

Gray's Anatomy is one of those iconographic textbooks that now transcend medicine [30]. It was originally the work of two Henrys, Henry Gray and Henry Vandyke Carter. One had a silver spoon handed to him by the reigning masters of medicine in London, and one came from a gifted artist's background [31]. One died early and his name is forever associated with anatomy; the other lived a long life, contributed greatly to medicine, and is lost forever except to those who love history and investigate trivial sidebars on old textbooks. It is a tale of two Henrys and of course urinary stone disease [32].

Henry Gray (1827–1861). Gray was a hyper-energetic, driven young scholar who died tragically after the second edition of his now famous anatomy textbook was published in 1861. Gray was born in London where he spent much of his young life. In 1845 he attended St. George's Hospital already famous for its surgery and it surgeons. In 1848 he won the coveted triennial prize of the Royal College of Surgeons as a third year student, essay entitled *The origin, connections and distribution of nerves to the human eye and its appendages, illustrated by comparative dissections of the eye in other vertebrate animals* [33]. In 1852 after just finishing his training, he was elected at age 25 to become a member of the Royal Society. His meteoric rise continued the following year, 1953, when he wrote a treatise *On the structure and Use of Spleen* where he utilized the services of another gifted St. George's pupil, Henry Vandyke Carter, who drew most of the illustrations for this paper [34]. Gray won the Astley Cooper Prize and 300 guineas for his efforts but gave young Carter no credit whatsoever. In fact, Gray appears to have stiffed Carter out of much needed funds for his medical education in for the medical illustrations [35]. This was a foreshadowing of their work to come and it appears that the young anatomists had learned nothing from the squabbles between Vesalius and Colombo nor Ruysch and Bidloo.

"*This work is intended to furnish the Student and Practitioner with an accurate view of the Anatomy of the Human Body, and more especially the application of this science to Practical Surgery*" [36]. Thus begins Henry Gray in the first edition of *Anatomy, Descriptive and Surgical* in 1858. Acrimony aside, Gray then thanks his co-contributor, "*The Author gratefully acknowledges the great services he has derived, in the execution of this work, from the assistance of his friend, Dr. H. V. Carter, late Demonstrator of*

Anatomy at St. George's Hospital. All the drawings, from which the engravings were made, were executed by him. In the majority of cases, they have been copied from, or corrected by, recent dissections, made jointly by the Author and Dr. Carter" [36]. Between pages 660 and 663, the anatomy of the kidneys is presented: "*The* ***cortical substance*** *forms about three-fourths of the substance of the gland. It occupies the surface of the kidney, forming a layer about two lines in thickness, and sends numerous prolongations inwards, towards the sinus between the pyramids of the medullary substance*" [36]. He follows the description of Morgagni by stating "*The* ***medullary substance*** *consists of pale, reddish-colored, conical masses, the* ***pyramids of Morgagni****; they vary in number from eight to eighteen*…" They proceed to discuss the known microscopic anatomy of the tubules and the glomeruli [36]. Bowman's, Malpighi's, and Bellini's works were known to them, but Henle and Golgi's were not done at this time. They continue, "*The* ***Malpighian bodies*** *are found only in the cortex substance of the kidneys. They are small rounded bodies, of a deep red color, and of the average diameter of 1/120th of an inch. Each body is composed of a vascular tuft inclosed in a thin membranous capsule, the dilated commencement of the uriniferous tubule*" [36]. The description of the tubules reflects the knowledge of the times, "*According to Mr. Bowman, the tubuli uriniferi commence in the cortical substance as small, dilated, membranous capsules, the capsules of the Malpighian bodies; they also form loops, either by the junction of adjacent tubes, or, according to Toynbee, by the union of two branches proceeding from the same tube; they have also been seen to arise by free closed extremities*" [36]. These observations are wrong but soon to be corrected by Golgi. Also missing from this first edition of Gray's was surgical approaches to the kidney or ureter. This was simply not done yet but was looming close at hand. They also avoid much discussion about perineal lithotomy, though the work was dedicated to Benjamin Brodie: "*To Benjamin Brodie, BART., F.R.S., D.C.L., Serjeant-surgeon to the Queen, Corresponding Member of the Institute of France, this work is dedicated, in admiration of his great talents, and in remembrance of many acts of kindness shown to the author, from an early period of his professional career*" [36]. They did describe urethral trauma and the perineal anatomy of urinary extravasation.

Henry Vandyke Carter

Henry Vandyke Carter (1831–1897) was the second Henry on the original Gray's Anatomy. He was born on May 22, 1831, to the famous watercolor artist Henry Barlow Carter. Henry was the eldest son and was educated at Hull Grammar School until he entered St. George's Hospital to study medicine in 1847 [37]. St. George's Hospital also was one of those epicenter institutions that was discussed in the "English School" in the chapter on founding fathers. Basic urinary chemistry and stone chemistry was certainly discussed with students at St. George's. He qualified for his M.R.C.S., L.S.A. in 1852. In June of 1853 he obtained a coveted fellowship in human and comparative anatomy at the Royal College of Surgeons where he primarily worked with J.T. Quekett but also the more famous Richard Owen. He also was a demonstrator in anatomy at St. George's Hospital until July of 1857 [37].

Henry came from a family of artists. Both his father and his brother were talented artists; his father was the more famous of the pair. Henry began to use his own artistic talents early in his medical career [35]. He began to work for Henry Gray and others in 1852 [38]. During this period, Carter did a series of anatomic illustrations for Gray's work on the spleen. There is evidence that the money that was expected to be paid to Carter from Gray did not materialize. There is significant evidence that tensions were high between the two, and the friendship that is often mentioned by be far from the truth [37]. In 1856 he commenced the illustrations for Henry Gray's Anatomy book. This was eventually published in 1858 [34].

In 1858 Carter joined the Bombay Medical Service and by May of that year he became the professor of anatomy and physiology at Grant Medical School. He also served as assistant surgeon in the Jamsetjee Jeejeebhoy Hospital [39]. He was clinically busy from 1863 to 1872 because he also was the civil surgeon at Satara. His interest in leprosy became significant and he asked for a furlough from India to study in Norway. He returned to India in 1872 and was deputed to Kathiawar to investigate leprosy [40]. In 1876 he became the director of Gokuldas Tejpal Hospital in Bombay. In 1877 he was appointed acting principal of Grant Medical College. Carter retired from service in 1888 and subsequently became Honorary Deputy Surgeon-General and Honorary Surgeon to the Queen. He died the following year of tuberculosis, on May 4, 1897 [41].

Carter's Stone Disease

On Carter's final return to England, he had several agendas. First and foremost might have been his health. He had contracted tuberculosis and came home to rest. But he brought work projects that never seemed far away for him. In addition, he had made a bad marriage while in India that was dissolved, and he finally met his soul mate in London and married. In June 1873 he published his book on stone disease, *The Microscopic Structure and Mode of Formation of Urinary Calculi* [42]. In his preface, he states that this project came to him in India and his own words are much more interesting: "*It appeared to the author, when he commenced these researches two or three years ago, at a small station on the Deccan plain of Western India, that a blank existed in medical literature which he might do something to fill up; and opportunity presented itself in a number of 'stone' cases, it was at once pursued with the valuable aid from others in a free and liberal supply of additional specimens*" [42]. Then, so reminiscent of his interactions with Henry Gray, Carter names every person who helped him from India and upon his return to England. He notes his debt to Dr. Beale's work in this area which we expand upon in the next section. In addition, he expounds upon Mr. Rainey's work in 1858 on seashells and "*molecular coalescence.*" He also lauds the previous work of William Ord, who like Carter was influenced by Rainey at St. Thomas's Hospital [42]. We will return in some detail to George Rainey's contributions in a later chapter.

Carter's textbook is relatively short and arranged in two parts. In Part I he focuses upon the microscopic structure of stones, particularly stones from patients in India. He uses the classification scheme of Wollaston in his approach to discussing the varying types, modified by Golding Bird. In Part II he begins his dissertation on the mechanisms of stone formation, not limiting himself to human stone disease. He then delves deeply into the hypotheses of Rainey and "*molecular coalescence*." Since Carter painstakingly credits everyone, there is no mention of an illustrator, so one is left to assume that he illustrated his own work. The plates that accompany the text are therefore most probably Carter's illustrations and they are beautiful works of art. Plates I and II are on uric acid stones (Fig. 15.1a, b). Plate III is on oxalate of lime stones (Fig. 15.1c). Plate IV is on unusual crystals and phosphates (Fig. 15.1d). The book is concise, specific, and clearly written to highlight his understanding of stones and their formation [42].

In the beginning he tells the reader that "*About one half of the specimens examined were submitted to inspection very soon after their extraction, but I do not know that in them, the internal appearances were in any way different from those observed in calculi, which had been kept for months or years*" [42]. He took copious notes about the histories of the patients who suffered these concretions, and he did have available one of the best microscopes he calls a "*polariscope*" to examine the various layers of these stones [41]. His method of examination was meticulous. He divided each of the stones in half; the nucleus was identified and each of the layers was examined separately and recorded. He stated that after a bit of practice that his "*microscopic analysis of urinary calculi is not only valuable, but that it is even more delicate than the chemical method; by its aid will be seen still more clearly than before, that no single urinary deposit long*

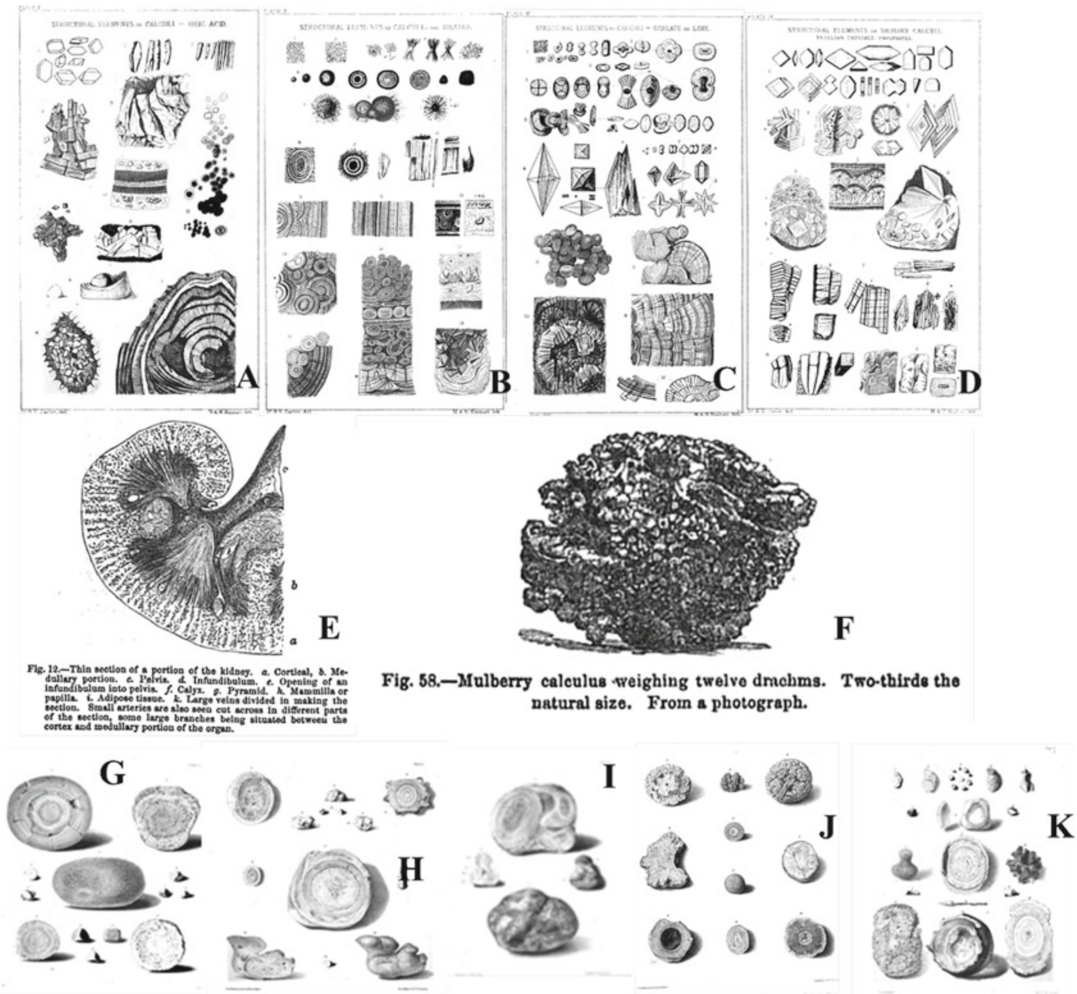

Fig. 15.1 Illustrations from Henry Vandyke Carter's 1873. *The microscopic structure and mode of formation of urinary calculi* (**a**–**d**) compared to Beale's *On Urine, Urinary Deposits, and Calculi* (**e**, **f**) and finally to Thomas Taylor's 1842 work on stones from the Royal College of Surgeons (**g**–**k**)

occurs alone, and there will be gained a more accurate conception of the renal structure of these hurtful concretions" [42]. His first chapter was about 80 stone specimens. There were two tables in this first section which serve to summarize his findings. In table one he gave the age of the patients, the duration of symptoms, the weight of the calculus(*i*), and then the details of the anatomy of each stone from nucleus, through layers and the outer crust. Table 15.2 is the summary of the system of classification that Carter used, basically separating stones into "organic" and "inorganic" categories using a Linnaean hierarchical scheme including order, genus, species, and chemical composition [42]. Uric acid was present in 36 % of the vesical calculi but only noted in 10 % of the nuclei. He noted urates in 62 % of the vesical calculi and in 56 % of the nuclei. He noted oxalate of lime to be the single, most common mineral in stones in 70 %. It was present in the nucleus in 30 % of stones [42]. He thought that it was unusual that no stones were wholly phosphate of lime in his Indian patients. Carter comes to four conclusions at the end of his microscopic work: "*It is evident that urinary calculi are not mere precipitates or aggregations of ordinary crystalline and amorphous deposits, held together by means of mucus, & c…Some*

Table 15.2 Modified from Hunterian collection by Mr. Thomas Taylor, 1842

1.	Uric acid	Discovered by Scheele	1776
2.	Urate of ammonia	Fourcroy and Vauquelin	1798
3.	Oxalate of lime	Wollaston	1797
4.	Cystic oxide	Wollaston	1810
5.	Xanthic oxide	Marcet	1815
6.	Phosphate of lime	Wollaston	1797
7.	Phosphate of Magnia and ammonia	Wollaston	1797
8.	Fusible calculus	Wollaston	1797
9.	Carbonate of lime	Brugnatelli	1819

specimens, indeed, display a special beauty of varied arrangement" [42]. His second finding was that stones have a surprising amount of animal materials in them. He believed that this biologic material forms the layers between minerals and is more common in the urate variety of stones. His main finding was the third conclusion. He believed that the main mineral composition was altered in some fashion by the actions of the biologic material present in stones themselves. He proposed the term "*sub-morphous*" to explain the crystalline oddities he observed and drew: "*For such structures I would propose the name '**sub-morphous**,' in contradistinction to the a-morphous, so called; separately, they have in this memoir been termed 'globules,' 'dumb-bells,' 'speroids,' 'laminae,' & c…*" [42] He also noted that these forms could be synthetically generated in the chemistry laboratory. His final conclusion was that stones do not form by accident, but their mineral nature of the nucleus, especially of oxalate of lime is significant. He would go on in the second portion of his work to address these findings.

In the second chapter he begins with a lengthy dissertation on stone formation. He begins with plants and their raphides. He notes that these are typically oxalates and phosphate of lime especially in the cactus [42]. He notes that agates arise from sponge organisms and that they too have some organic structure combined with the oxalate of lime. He arrives at the work of Rainey and Harting looking at shell structure and the layering that occurs in stones is similar. He notes that the sodium urate of gout appears first in the cells of the cartilage serving as foci of deposits referred to as "sclerites" [42]. This is similar to the production of the raphides in the plant cell. His full attention is now given to Rainey's molecular coalescence. He goes into quite some detail, but simplistically the mixture of proteins with the crystals produces spheroids that form various configurations based upon the local conditions: "*Should the solutions be dense, globules form slowly; and should they be of less specific gravity, these may form within a few hours; if the saline solutions and colloid are at once mixed together, the globular and dumb-bell forms which appear are small, of uniform size, and stationary; if admixture be effected slowly and gradually, the globules are more perfect, and continue to grow for months; in a dense colloid the globules are fully rounded, in an attenuated medium there is a tendency to the production of crystals, and a gradational series of forms from crystalline to sub-morphous may appear in accordance with a corresponding in the character of the colloid*" [42]. Modern crystallography is rarely more elegant than this description. He continues to speculate that there appears to be secondary modification of the crystals into rhomboid plates of mineral and organic phases; he refers to these as "fascicles of crystals." He believes this is how the stones grow and propagate. Let's quote him extensively now, "*Seeing the comparative infrequency of stone, it is apparent only under certain circumstances do the more insoluble ingredients of the urine assume, or rather retain, the forms in which calculi arise, and by which they increase; hence it is the observed facts bearing directly on this subject are as yet so few, and in this dearth of positive knowledge any remarks I may offer will have more or less influence, according as they appear rational or only vague*" [42]. And so Henry Vandyke Carter joins the pantheon of early stone philosophers.

Beale- Anatomy, Urine, and Microscopes

Lionel Smith Beale (1828–1906) is the person to whom Vandyke Carter alluded to in his treatise on stone disease. He was one of those prolific surgeons who was educated in London, wrote volumes about a wide variety of scientific concerns, and corresponded with Charles Darwin [43]. He was a major proponent of the use of the microscope and taught and wrote extensively about this apparatus. Beale's father was a surgeon in London, and his son was to follow his path, attending King's College School. He matriculated to London University with honors in chemistry and zoology. He worked in anatomy for two years at Oxford prior to becoming a resident physician at King's College Hospital. In 1852 he established a laboratory and began to teach private courses using the microscope. At the age of 29, he was elected F.R.S. and F.R.C.P. at age 31 [43]. He wrote a number of books on disease germs and most significantly on the microscope. *The Microscope in Medicine* first published in 1854 went through four ever expanding editions and was in possession of Sir William Osler [44]. In his obituary notice on Beale, Osler wrote: "*The influence of Dr. Beale as a scientific investigator and as a clinical physician was much more widespread than perhaps was recognized in London or Great Britain at large…His two well-known books* ***How to work with the Microscope*** *and The* ***Microscope in Medicine*** *were of the greatest service to two generations of medical students*" [45].

Beale would never be known for his succinct titles, even though his microscopic works would beg one to differ. His work on stone disease however was quite another thing. *On Urine, Urinary Deposits, and Calculi: Their microscopical and chemical examination, including the chemical and microscopical apparatus required, and tables for the practical examination of urine in health and disease; The Anatomy and Physiology of the Kidney, with upwards to sixty original analyses of the urine in disease, and general remarks on the treatment of certain urinary diseases* was published in 1861 [46]. Although this work was not just about stone disease, it was more an atlas of urinary sediment in health and disease; it did cover the analysis of stones but does not detail the formation of stones like Carter's work. Beale did include the work of Henry Carter in his textbook as well as quoting most all of the founding fathers of stone chemistry. We will look at his section IV "*Of the Origin and Formation of Calculi*" in the chapter on urinary calculi, pages 349–360 [46]. He stated "*Whenever there is a tendency to the precipitation of any of the slightly soluble constituents of the urine in an insoluble form before the urine has left the organism, one of the conditions most essential to the formation of calculus is present*" [46]. This is a modern notion of supersaturation. He continued discussing what is now heterogeneous nucleation: "*If the urine alters in its character, different substances may be deposited; thus, oxalate of lime may form the nucleus of the calculus; and, after this has reached a certain size, the deposition of the oxalate may give place to that of uric acid*" [46]. He as did Carter concentrated on the formation of the nucleus as the key event in stone formation, and he digressed by discussing the role of foreign bodies that could start the process in the bladder: "*Any solid matter may form the nucleus of a calculous concretion*" [46]. He also speculated that the calcium oxalate within the nucleus of most stones was the precipitating event: "*In all probability neither the phosphate nor the uric acid would have been precipitated had not the oxalate been present in the first instance. It is not too much to say that if the latter had not remained for some time in the uriniferous tubes and gradually increased in size, no calculus would have been formed …*" [46]. This same problem will get addressed in the modern era by Birdwell Finlayson, retention times, and the clearance of concretions from the kidneys. Beale's conclusion on the prevention or treatment of calculus disease was also poignant: "*I have already adverted to the importance of increasing the quantity of fluid taken by persons who suffer from certain varieties of urinary deposits. This principle has been fully recognized by Prout and many practical physicians who have had experience in treating cases of this class; but the remedy, perhaps from its very simplicity, has certainly not received the attention at the hands of many practitioners that it deserves*" [46].

Conclusions

Now it is time to return to John Hunter's stone collection and the natural history of his obsessiveness. Hunter's collection joined with those of his nemesis, Sir Everard Home his brother-in law [25]. In 1842 the Royal College of Surgeons in London published an extensive treatise of all types of stones, written by Mr. Thomas Taylor, a surgeon and member of the Royal College [47]. He begins this treatise by laying out the reasons for the division of this complex work: "*The present Volume contains a Descriptive and Illustrated Catalogue of the different kinds of solid bodies found in various cavities of the animal body, and which are unconnected with living textures. It is divided into three parts*" [47]. It is the first portion of this work that is most interesting to a treatise on history of stone disease, entitled Concretions occurring in the Urinary Organs. Each part was also divided into the human and "comparative series," meaning different animals including mammals, birds, reptiles, and fishes. These were presented as a series of cases in each class of stone type that was determined by chemical methods. Illustrations were prepared of especially interesting stone cases (Fig. 15.1g–j). The organization scheme followed that of Wollaston's with modifications by Golding Bird. A total of 649 calculi were included in this analysis and presentation. Uric acid formed the nucleus in 5:12, urate of ammonia in 4:13, and oxalate of lime in 1:6¾. Stones were considered mostly homogenous solitary composition in 315 (about ½) of the stones making compound stones equally likely. He also noted, "Th*e accuracy of the **general law** laid down by Dr. Marcet, that the phosphatic diathesis is never succeeded by any other, is fully borne out by the examination of this collection. There is no instance in which the Phosphates form the nucleus of a calculus, and only one in which they have been succeeded by oxalate of lime*" [47]. He begins the presentation of the case histories with a bit of history of stone disease, touching on the founding works of Scheele, Paracelsus, van Helmont, and Marggraf. He touches upon the works of Pearson, Fourcroy, Vauquelin, Wollaston, and Marcet. He concludes his history with contributions of Prout, Brugnatelli, Brodie, Yelloly, Liebig, and Wöhler. He summarizes the history of stone disease with a simple table that presents the various stone types, chemically with the person who is attributed with its identification. Taylor really adds no fundamental advancements to stone knowledge, but the illustrations of the stones themselves in the monograph are the most artistically pleasing of all publications to this date; in fact the xanthine stone rendition saves for all time this truly rare stone first described by Marcet (Fig. 15.1k). Anatomically speaking this was its major claim to fame.

Concluding a chapter on anatomy, autopsy, and stone disease should have a special story fitting this topic. We have mentioned the friction between Henry Gray and Henry Vandyke Carter; now let's turn our attention to the first edition of *Anatomy, Descriptive and Surgical* and look at the pettiness or vanity that prompted Carter's withdrawal from mainstream medicine and his flight to India. Figure 15.2 represents the frontispiece copy that is carefully kept of Henry Gray's proofs to his publisher at the Royal College of Surgeons of Edinburgh. The publishers, J. W. Parker and his son, were aware that Carter had received only ½ fee for his work and had been excluded from royalties which Gray was to receive £150 for every 1,000 books sold [35]. Gray was not done in his self-promotion; in the page proofs he slashed two lines through Carter's name with his new M.D. title and "*Professor of Anatomy, The Grant College, Bombay*." Next to this he wrote "*to be omitted*." Finally he wrote "*Type size of the name below*" [35]. Gray demanded that Carter's name be in a smaller font and moved further down from his name at F.R.S. title. Anatomy's god was a jealous master and Henry Gray did little to demonstrate his "friendship" to his coauthor and illustrator.

William Harvey loved to dissect bodies, and in 1635 he had the opportunity to perform an autopsy on the most famous man of his era, Thomas Parr. Parr was a yeoman farmer who allegedly lived to the age of 152 and was the oldest known human being. During the autopsy Harvey noted the rather youthfulness of Parr's organs. But it is the kidneys

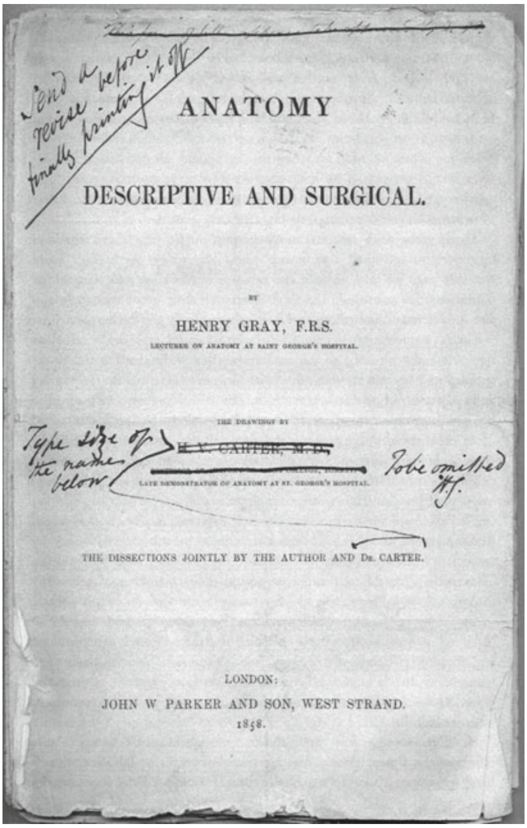

Fig. 15.2 The "proofs" title page from the 1858 edition made in June 1858, annotations by Henry Gray

that are of interest to us here, so in Harvey's own words, "*His kidneys covered with fat, and pretty sound…Not the least appearance was there of any stony matter either in the kidneys or bladder. His bowels were also sound, a little whitish without. His spleen very little, hardly equaling the bigness of one kidney. In short, all his inward parts appeared so healthy, that if he had not changed his diet and air, he might perhaps have lived a good while longer*" [48].

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16 The Stone Hospital and Stone Treatment

Introduction

People who have been sick in past times have had few options until the development of hospitals. Care was typically provided for in homes of families or relatives. But hospitals were originally not for the sick, but for the poor, the deformed, the handicapped, and orphans [1]. The "hospital" itself is derived from the Latin root *hospes* implying a guest. The noun *hospitium* would imply a guesthouse [2]. Every hospital, however, performed its function in some sort of building or domicile. Hospital history is intimately tied to the beliefs, social, economic, and even the military aspects of the community in which they occur. The images of these early hospitals are mainly now artistic [3]. A print of the late sixteenth century by Philippe Thomassin is entitled "*The Fourth Work of Mercy is to visit the sick.*" Yet hospitals clearly existed prior to the Middle Ages and some of them performed as significant medical centers. In Ancient Greece the healing centers were intimately associated with places of worship, so the cult of Asclepius were centers called *Asclepieia*. About the same time in India and Southeast Asia, known centers for treating the sick were also recorded. The first large-scale hospitals that evolved specialty care and teaching of health care developed in Persia with the city of Jundishapur being founded in 271 CE. There hospital developed in one of the first epicenters for medical learning in ancient times [4].

Troy, New York, is a city of 55,000 people in upstate New York located along the Hudson River at the convergence of the Mohawk. It is a city of surprisingly rich cultural heritage, and it was home to New York State's first hospital outside New York City, a city immortalized by the famous surgeon, writer, and stone sufferer Richard Seltzer in his "*Down from Troy*: *A Doctor Comes of Age*" [5]. The fiftieth anniversary Jubilee celebration of Troy's Hospital brought William Osler to the city as the keynote speaker. It is one of Sir William's less well-known addresses and was delivered on November 28, 1900, at the Old Troy Hospital in the Collar City [6]. Troy's reputation at this time carried more luster than in fact the town then held. By the time Osler visited the Old Troy Hospital on its Golden Jubilee to address the town, there was significant feeling of an impending depression. Osler's emphasis of his lecture was centered on the hospital's link to its community, and these were fortuitous as the ties binding the medical staff to the hospital and to the town cannot be fully appreciated except in retrospect. Both the town and the hospital would fall before a score of years passed [7].

Osler commenced his comments with remarks from Thomas More's *Utopia* [8]. "*But the first and chiefly of all, respect that he has had to the sick, and be cured in hospitals….*" This was the key element of his talk, it formed the foundation for which he would go on to speak throughout his address, and it tied the city's future to that of the hospital and its community. He switched in his next statements to the ideas of the *Good*

M.E. Moran, *Urolithiasis: A Comprehensive History*, DOI 10.1007/978-1-4614-8196-6_16,

Samaritan, "*not so the problem of the sick, poor, which charity answers with the smile…*" [6]. Osler proceeded to his main theme, "*about the hospital centers all that is best and highest in the profession of medicine…in it…we doctors live and move and have our beginnings…*" [6].

This address represents a classic Oslerian oration. He began with a theme from the classical author, in this case Sir Thomas More and *Utopia* [7]. Osler next moved into his "old saw" about the ability of good men in medicine to contribute greatly. Neither Osler nor his audience was fully aware of the financial peril that both the city and the hospital were facing. This was particularly eerie in the light of his choice of *Utopia*. In *Utopia*, More painted the picture of a community no longer strapped by financial considerations and money. The hospital was the classic reference in his work where he poignantly referred to man's potential greatness, especially when removed from financial considerations [7].

The Old Troy Hospital represents a metaphor to the story of hospitals in general. The rise and fall in the communities that they serve certainly places them in the context of the culture [9]. But disease itself can and has influenced the function of hospitals. Stone disease has certainly played a role in the development of institutions for the sick and in specialty hospitals themselves.

Hospitals and Stone Disease

It is possible that in the entire history of hospitals, only infectious diseases have had a more profound effect upon hospital development than bladder stones. Bladder stone disease had been of more profound incidence prior to the Industrial Revolution than kidney stones. We have discussed previously some of the work, particularly in England during the eighteenth century, that indicated a sharp upward turn in the development of urinary stones, particularly bladder stones. To put into perspective the seriousness of the stone problem in the Industrial Age England, we have previously mentioned Dobson's 1779 "*Commentary on Fixed Air*" [10]. In the discussion on stone disease, Dobson reports upon a statistical inquiry which he conducted into the incidence of stone in various parts of England. The number of patients with stone admitted to the Norwich Infirmary was 30 times greater to that admitted to Cambridge Hospital. He reports that in Gloucester, Worcester, Hereford, and Exeter hospitals, there was 1 stone patient among 394 admissions. In the northeast including Newcastle, York, Leeds, and Manchester, there was 1 stone patient per 420 admissions. In Liverpool, Chester, Shrewsbury, and North Wales, the ratio was 1:3,223 [10]. Even Sir Thomas Browne, the most famous physician of the region, was aware of this phenomenon. In fact, a little church at Stoke Holy Cross just four miles from Norwich has a memorial for Reverend Thome Havers who also performed lithotomies and died in 1719 [11].

Norwich is an inland port town in East Anglia also historically referred to as the Cathedral City. Norwich has long kept meticulous records, so chronologically it has become a historian's dream. The first barber-surgeon recorded is John Belton in 1163, and the first surgeon was Randulph de Morlee in 1288, and he might well have had advanced training [12]. John Caius (1510–1573) was born in Norwich, educated at Gonville College, Cambridge, prior to attending the medical school at Padua. He lived in the same house as Andreas Vesalius and returned to become the first lecturer in anatomy at Cambridge (though there is some thought that Thomas Vicary did so as well) [12]. The 1684 Ordinances of Norwich began to regulate the quality of the barbers and surgeons in the city. This required that the surgeons who wished to practice were subject to examination and codified the apprenticeship [13].

King Henry VIII had already codified this process in 1511 when he placed the authority to license surgeons and physicians into the hands of the Bishop of London and the Dean of St. Paul's. This same authority was also distributed to the bishops and archbishops in the dioceses [14]. So a system was well established with control by apprenticeship, licensing by bishops, approved by the city fathers, and monitoring by the Barber-Surgeon's Company. By 1745 the surgeons formally separated with the barbers and the Royal College of Surgeons of England was attempted.

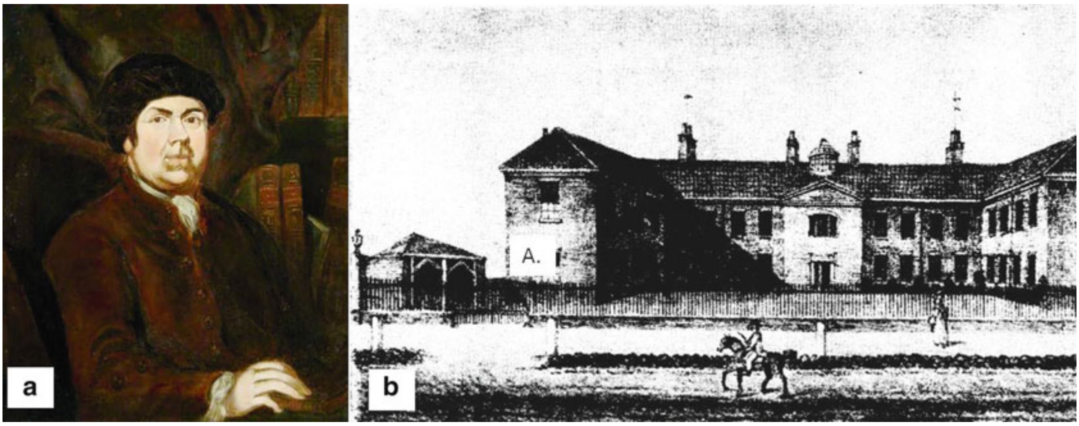

Fig. 16.1 (**a**) Benjamin Gooch and (**b**) the Norfolk and Norwich Hospital

More on this will follow after looking into one of the founding fathers of the Norfolk and Norwich Hospital. Benjamin Gooch (c. 1707/1708–1776) was a leading lithotomist in the Norfolk region in the first half of the eighteenth century (Fig. 16.1a) [15]. He was born to the Reverend Benjamin Gooch in Ashwellthorpe. He was apprenticed to a leading Norwich surgeon, David Amyas, who later recorded that Gooch was "one of the best surgeons I ever knew." He probably went to London for further training and returned to work with Robert Bransby of Hampton, another lithotomist. He married Bransby's daughter, Elizabeth, and they in turn had just one daughter who they also named Elizabeth [15]. On Bransby's side of the family, Gooch's nephew would be Astley Cooper. Gooch's daughter, Elizabeth, almost married Edward Thurlow who later became Lord Chancellor of England (formerly Thomas More [*Utopia*] and Francis Bacon [*The New Atlantis*]) and who lobbied hard to defeat the first attempt to establish the College of Surgeons. Elizabeth chose instead to marry Gooch's assistant John D'Urban a surgeon and M.D. from Edinburgh [15]. Perhaps Lord Thurlow had a personal vendetta against surgeons and lithotomists when he lobbied against their charter to the House of Commons [13]. Gooch performed a number of lithotomies by either the median or lateral approach. He also was one of the first surgeons to remove a bladder stone in females through the vagina. Between 1772 and 1909 35 cases of bladder stone were reported in females using a dilation of the urethra technique also developed in Norwich [15]. Yelloly wrote up this technique in 1815 [16].

Another surgeon John Harmer reportedly performed over 170 lithotomies by 1746. Gooch assisted Harmer on a fateful case in the same year, a 48-year-old gardener from Portland, near Norwich had a 12 by 8 in., 14½ apothecary ounce (450 g) bladder stone removed via a Marian lithotomy [17]. By 1757 at about the age of 50, Gooch suffered ill health and went to Bath for treatment by Jeremiah Pierce. He slowly recovered and returned to surgical practice by 1760. During his time off, he published a scholarly work on surgery, *Cases and Practical Remarks in Surgery* [18]. He dedicated the book to his friend and squire, William Fellowes, who opened the first cottage infirmary at Shotesham. "*It was your erecting an Infirmary for the benefit of the poor which gave me an opportunity of making some of the following observations in surgery; and when the opinion of my friends inclined me to publish them a sense of my obligations to you called for this profession of my gratitude*." The one-volume first edition was popular enough to prompt a two-volume second edition in 1766 [15].

Benjamin Gooch would parlay this interaction with Fellowes into founding the Norfolk and Norwich Hospital in 1772. Gooch went to London and visited the hospital to draw up plans based on the latest designs. In August 1770, in an open meeting at Guildhall, Norwich, the project of the hospital and creation of a subscription fund to purchase a site for the hospital was approved (Fig. 16.1b). The six-man committee included Gooch, William Fellowes, and the Reverend Samuel Cooper (Sir Astley's father). Reverend Cooper was selected to draw up the first rules and orders for the conduct and government of the hospital [15]. In Gooch's second edition, he came out with a third volume, called an Appendix. He dedicated this volume to the Governors of the Hospital "*as a testimony of the honour done me in electing me as a consulting surgeon*" [15]. Gooch never was on the active staff and never operated at the hospital. But a portrait of him hangs in the medical staff room. The Gooch Prize is given to junior medical staff, and the main lecture hall is appropriately named Gooch Hall. The Hospital originally had 100 beds and was a "state-of-the-art" institution. The number of beds was increased to two hundred beds when the hospital was rebuilt in 1879–1883 [17]. All patients admitted were recorded, and the hospital kept a special register for stone cases. The original register has not survived but the Reverend C.J. Chapman presented to the hospital a vellum-bound book containing a copy of the original entries in 1819. This historical legacy is called "*A Record of the Stones Patients in the Norfolk and Norwich Hospital. Not to be Taken Away*." A second register of the stone patients was begun called "Norfolk and Norwich Hospital Catalogue of Calculi 1909," which documented the stone series until the very year that the stone epidemic subsided. On February 20, 1773, the hospital had been opened for a mere 7 months when the governors voted to provide the "*Apothecary do provide a suitable nest of drawers to deposit the stones extracted in this House, in order to show to strangers, and to be referred to occasionally-and none suffered to be taken away*" [17].

"The Norwich School of Lithotomy"

The Norfolk and Norwich Hospital in 1771–1772 followed the successes and failures of its constituent community but is vitally important to a history of stone disease. Sir Astley Cooper spoke of this institution in 1835 "*the degree of success which is considered most correct is that taken from the results of the cases at the Norfolk and Norwich Hospital*." Alexander Marcet wrote about this institution in 1817 "*In my enquiries I have met with great disappointments…it will appear scarcely credible that in the larger hospitals in London, St. Bartholomew's, St. Thomas's, Guy's and the London Hospital, no regular or at least no ostensible records of the cases of lithotomy which occur in them should be preserved. It is with great pleasure, however, that I am enabled to mention one striking exception to this unaccountable oversight in public hospitals. The Norfolk and Norwich Infirmary in this and several other respects, stands as a model of regularity and good management*." Jean Civiale in Paris described "*labelle et riche collection de Norwich*" in 1863. Sir Henry Thompson wrote also in 1863 called Norwich "*the most perfect and complete record, literally graven in stone, that the world possesses of calculous experience*" [17].

William Hyde Wollaston, who became the founding father of British stone chemistry, was born to the vicar of East Dereham in Norfolk. Wollaston communicated with another physician from Norfolk regarding stone chemistry, Dr. Henry Reeve. Reeve (1780–1814) was born in Suffolk and became a pupil of Philip Meadows Martineau (lithotomist* see Table 16.1). He attended medical school in Edinburgh. Martineau returned to Norfolk and Norwich Hospital and performed first chemical analysis of the stone collection. This sadly was lost. His younger brother suffered from stones and was operated upon at the age of five. His stone too was added to the collection, but he suffered from recurrence and eventually died of his stone disease. Reeve sent his brother's first stone to be chemically analyzed to Wollaston because of its unusual physical characteristics, and it turned out to be the second cystine stone to be reported [17]. Reeve sadly died at the young age of 34 with so much future potential. The Reeve collection, his letters, and his stone analysis have all disappeared but were recorded by Sir Peter Eade in 1900. This discrepancy however was corrected by the work of John Yelloly (1774–1842) who performed a

Table 16.1 Surgeons who operated at Norfolk and Norwich Hospital from 1772 to 1909, modified from Shaw (* discussed in detail in this chapter, ^ discussed in previous chapter)

Surgeon	Years	Number of operations
W. Donne	1772–1800	173
W. Palgrave	1772–1775	5
J. Alderson	1772–1791	69
E. Rigby	1790–1814	106
P.M. Martineau*	1793–1828	149
E. Colman	1803–1812	44
W. Bond	1813–1826	45
W. Dalrymple	1815–1838	90
J.G. Crosse^	1826–1849	52
H. Carter	1830	2
B.H. Norgate	1831–1857	57
J.G. Johnson	1838–1847	10
G.W.W. Firth	1849–1878	58
W.P. Nichols	1850–1872	75
A. Dalrymple	1852	2
W. Cadge	1857–1895	240
T.W. Crosse	1858–1895	77
C. Williams	1873–1906	73
M. Beverley	1879–1892	21
S.H. Burton	1890–1904	57
H.S. Robinson	1890–1904	37
D.D. Day	1896–1909	16
Sir H.A. Balance	1898–1909	14
E.W. Everett	1907–1909	6

second and more detailed analysis of the Norwich stones which he presented in two papers to the Royal Society in 1829 and 1830. Yelloly attended Edinburgh and then the London Hospital from 1807 till 1818 [19]. He became friendly with Wollaston's protégé, Alexander Marcet (one of the founding fathers of stone chemistry) and helped him found the Royal Medical and Chirurgical Society in 1805. He was a bibliophile and started the Society's library and was elected as a fellow in the Royal Society in 1814 [19]. He acknowledged the help in these analyses by William Prout (another Wollaston-mentored physician) and Michael Faraday. It is of historical interest that Lonsdale and Mason have used modern microscopic crystallographic and X-ray diffraction methods on this same stone collection to verify that the stones of the children are in fact similar to those of endemic disease regions of the world today, such as Thailand, Turkey, and India, which are conclusively associated with poor diet and the formation of ammonium urate stones in the bladder [20, 21].

Early in the development of the bladder stone center, Edward Rigby (1747–1822) came to Norwich at the age of fifteen and apprenticed with David Martineau. He was appointed as assistant surgeon at the age of 24 and went on to obtain his medical degree. He served the hospital as physician and surgeon for 49 years performing 106 lithotomies [17]. Philip Meadows Martineau (1752–1829) joined Donne and Rigby at the hospital following in the footsteps of his father, also a lithotomist who trained Rigby, David Martineau. Martineau gained wide acclaim for his surgical technique. Astley Cooper mentioned that "*no surgeon in London, I am certain, can boast of similar success and in Paris he was spoken of as 'le lithotomiste le plus eminent et le plus heureux de son époque'*." Martineau performed 149 lithotomies with a mortality rate of only 12.5 % (or about 1/8), and he described his own modifications of Cheselden's technique [17]. William Dalrymple (1772–1847) joined Martineau after training at Guys' and St. Thomas's Hospitals under Astley Cooper and Henry Cline. He performed ninety lithotomies over his 27-year career as staff at the hospital. These men were conscientious and worried about the patients they were entrusted. Edward Copeman, a young house surgeon, reported that Dalrymple stated "*I have often heard him say that he was not able to sleep the night before he was to perform a lithotomy; although in such cases his success was great*" [17]. Dalrymple's reputation was such that he was called to testify for a surgical defendant at Guy's hospital in 1828, Bransby Cooper. This nefarious small bladder stone still is in the Gordon Museum of Guy's Hospital, and we'll talk about the owner later on. John Green Crosse (1790–1850) was appointed to the surgical staff in 1823 and often assisted Martineau at lithotomies (holding the staff). Crosse studied in London, Dublin, and Paris prior to coming to Norwich [17]. He was awarded the Jacksonian Prize of the Royal College of Surgeons of England in 1833 for his essay

"*The Formation, Constituents and Extraction of the Urinary Calculus*" [22]. Crosse included in his references over 2,700 publications which was a monumental task. He was elected a fellow in the Royal Society. The final surgeon of note will be William Cadge (1822–1903). He studied medicine at University College Hospital and became the assistant to Robert Liston. He returned to Norwich because of ill health in 1854 and was appointed to the staff. He gave a summary of the outcomes at the 1874 British Medical Association meeting and the Hunterian lecture before the Royal College of Surgeons of England in 1886 [23]. He performed 240 lithotomies at the hospital, the greatest number by any surgeon, and at least 144 private surgeries outside of the hospital [17]. Others followed in the tradition of the Norwich lithotomists. Though several types of surgery were employed throughout these years, most were Cheselden's modified lateral approach (about 75 %). In 1936 Sir D'Arcy Power noted that the lateral lithotomy literally defined the successful surgeon. But by then, the big surgical procedures and the perineal route were becoming a subject of historical interest only [24]. Details of the history of surgical intervention will be developed later in this book.

Mr. Cheselden

William Cheselden (1688–1752) is considered one of the greatest surgeons of all time, and he is particularly relevant to this discussion because of his interest in bladder stone surgery (Fig. 16.2a). Cheselden was born at Burrow on the Hill, Somerby, in Leicestershire on October 19, 1688. He was the third child and second son to George Cheselden, a farmer, and became apprenticed to James Ferne, a young surgeon at St. Thomas's Hospital, at the age of fifteen [25]. While a student, William lived in the house of William Cowper, the famous anatomist. He probably attended anatomy lectures of Rolfe and Cowper. He finished his apprenticeship and became a freeman in the Barber-Surgeons Company in 1710. On October 8, 1711, he presented a 36-page syllabus for teaching anatomy courses in London and presented a paper to the Royal Society on some bones found in the ancient Roman site of Verulamium; he was only 23-years old. Cheselden's fortunes continued to rise, he married Deborah Knight in 1713, and he began to apply to St. Thomas's for a vacant surgical position. At age 30 he was finally chosen to fill a spot as assistant surgeon but he rapidly became full surgeon. He moved his young family from Cheapside to Red Lion Square and remained on the acting staff of St. Thomas's for 17 years [25]. Cheselden published his first book about his anatomical observations, Anatomy of the Human Body, in 1713 at age 25 [26]. This book sold well and was illustrated with 40 excellent engravings which were the work of Gerard van der Gucht [27]. His prowess and surgical skills had already become legendary, and accounts of his surgical techniques were written up by Dr. James Douglas in 1731. Cheselden kept accurate records of his

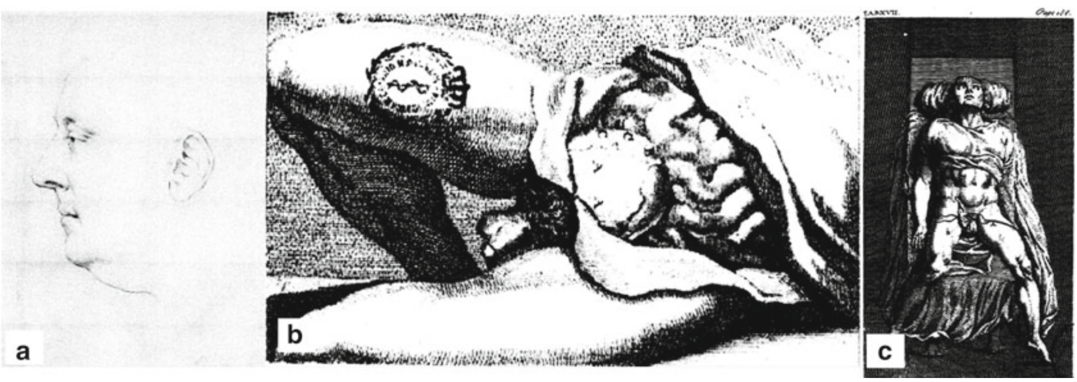

Fig. 16.2 Illustrations from Cheselden's first book on the High Operation. (**a**) Graphite portrait of William Cheselden. (**b**) Plate IV of pertinent anatomy. (**c**) Plate XVII showing patient in position for the High Operation

cases and his mortality rate was below 10 % and in children less than 10 years of age it was a mere 3 %.

In 1723 Cheselden published his first treatise on stone surgery, *Treatise on the High Operation for Stone* [28]. This book was also illustrated by the artist Gerard van der Gucht and contained 17 beautiful copperplates (Fig. 16.2b, c) [27]. In this book Cheselden presents his experience with the suprapubic cystolithotomy, and it represents his experience prior to learning the lateral lithotomy of Frere Jacques and Rau. Cheselden performed the perineal lithotomy by the Marian approach from 1720 to 1722. Between 1722 and 1725 he switched to the suprapubic method which was reintroduced by John Douglas (the pouch of Douglas; c1680–1743). Douglas also published a book on his technique in 1720 Lithotomia Douglassiana. It never succeeded. The suprapubic cystolithotomy was originally performed by Pierre Franco of Lausanne in 1561 [29]. Cheselden in his preface to the *Treatise* dedicated it to Dr. Richard Mead, fellow of the London College of Physicians and member of the Royal Society for the encouragement he received from him. He also specified that James Douglas had communicated to the Royal Society on an anatomical basis for performing a suprapubic lithotomy without pain in 1717–1718. He noted that Douglas' brother John had performed it but he does not include the date. Cheselden also mentions the work of Rosset and Pierre Franco. Cheselden continues that he is aware that he is not the originator of this method and had no intention of usurping this honor; he merely intended to present it with his modifications [28]. Another book was published in 1723 entitled *Lithomous castruatus; or mister Cheselden's Treatise on the High Operation, thoroughly examin'd and plainly found to be Lithotomia Douglassiana, etc., under another title: in a letter to Dr. John Arbuthnot, with an appendix, wherein both authors are fairly compar'd, to which is added a word of advice to surgeons*. This work was signed by a Robert Houston, perhaps a nom de plume by John or James Douglas [27].

In 1725 without anesthesia, Cheselden abandoned this approach for the operation of Jacques de Beaulieu (1651–1714) over the next 2 years. Cheselden had learned all that he could thirdhand from J.J. Rau's pupil Albinus. Rau's secrecy even limited the knowledge of Albinus, so Cheselden was forced to reconstruct the anatomical approach himself by studying the anatomy of the perineum [29]. Then in 1727 he introduced the technique of the lateral lithotomy which became named after him by publishing "Lateral Operation for Stone" [30]. Frere Jacques's operation now had an anatomical basis for guidance and every surgeon could now understand and master this technique (or not as we shall see) [31]. The controversy did not end there however, and the Douglas's claimed some precedence here as well. James Douglas published his *History of the Lateral Operation for the Stone* in 1726 [32]. Five years later, Douglas added an appendix entitled "*An appendix to the history of the lateral operation for the stone, containing Mr. Cheselden's present method of performing it.*" In 1731, Douglas appears to have come to peace with his colleague. Intriguingly, the illustrations to Douglas' book include some now famous engravings of Cheselden's instruments by none other than Gerard van der Gucht! [27] Also one final irony is that the French Académie des Sciences appears to have forgotten that the original description of the surgery and demonstrations by Jacques Beaulieu in Paris in the 1690s and sent Morand to London to learn from Cheselden. This started their lifelong friendship.

Cheselden became a fellow in the Royal Society. He became an honorary member of the French Academy of Sciences in 1729. He became the first foreign member of the French Royal Academy of Surgery in 1732. He was appointed as surgeon to Queen Caroline, wife of King George II. He also was appointed as lithotomist to Westminster Infirmary and to St. George's Hospital when it opened in 1733 [31]. In that year he also published his *Osteographia* which he had been preparing for years [33]. In 1737 Cheselden took the post as surgeon to the Royal Hospital Chelsea. Here he began to be more politically active, and with the aid of his son-in-law Dr. Charles Cotes on December 20, 1744, "*the Gentlemen on the Surgeons side made known their desire of being separated from the Gentlemen on the Barbers side, and produced a case intended to be offered to the Honourable House of Commons praying such separation*" [14].

This of course was first voted down secondary to the active lobbying of the Lord Chancellor Thurlow's negativity. The bill became law on May 2, 1745, and Cheselden's friend Randby became the first Master of the new Surgeon's Company. Cheselden did become Master in the second year while living at the Royal Hospital, Chelsea [13]. Cheselden was one of the experts on stone disease that was called in to see Sir Isaac Newton during his last illness. He suffered as only stone sufferers can, and Cheselden could offer no surgical alternative because of his age and severity of illness [31].

John Yelloly

John Yelloly (1774–1842) was born at Alnwick, Northumberland, on April 30, 1774, the youngest of seven children. He attended the University of Edinburgh and graduated with his M.D. in 1799. He went to London Hospital where he remained until 1818. Yelloly became close friends with Alexander Marcet, one of the founding fathers of stone chemistry, and he helped found the Medical and Chirurgical Society in 1805 [19]. In addition, he and his wife became very close with Sir Astley Cooper and maintained contact with them throughout their lives. Cooper and Yelloly were conspirators together in 1834 when they visited Lord Normandy to present the successful application for a Royal Charter for the Medical and Chirurgical Society to become the Royal Medical Society [19]. Yelloly was independently wealthy and he had no reason to practice, but he moved to Norwich in 1818 and became a physician at the Norfolk and Norwich Hospital in 1820. He probably became interested in the much lauded Norwich collection of stones via his interactions with Marcet. He presented a series of two papers in 1829 and 1830 to the Royal Society on stone disease. He published one pamphlet in 1837 *On Arrangements connected with the Medical Relief of the Sick Poor*. He also presented seven papers to the Royal Medical and Chirurgical Society, two dealing with paralysis from brain tumors; ironically he too died of paralysis from being thrown from his horse in 1842 [19].

Yelloly's first paper on the Norwich stones is entitled *Remarks on the Tendency to Calculous Diseases; with Observations on the Nature of Urinary Concretions, and an Analysis of a Large Part of the Collection Belonging to the Norfolk and Norwich Hospital* [34]. In part one of this paper, Yelloly concentrates on the incidence of this disease among the county of Norfolk. He began his dissertation by extolling the efforts of Benjamin Gooch. He warmed to his theme giving statistics, the hospital had been opened for a mere 56 years and 649 lithotomies had been performed, "*more than 11½ per annum*" [34]. Stone disease represented 1/40 hospital admissions, and he calculated the incidence in the county to be 1/34,000 inhabitants (575 patients out of 351,000). He calculates that those living in the city of Norwich are even more at risk of stone disease 1/21,000, and he proceeds to look at individual areas such as Lynn, Yarmouth, Taverham, Tunstead, and Walsham. He looked at the change in the population during this time and noted that the proportion of calculous cases had actually diminished as the population increased. He quoted the works of others who had also looked at the Norwich numbers, Dobson, Marcet, and Smith. He also tackles Copland Hutchison's assertion that the "*sea-faring life being remarkable for the comparative infrequency or urinary calculi*" [35]. Yelloly then looks at ages of life and notes a trend for more children having stones in the metropolitan city, than those rurally in the country. He also presents the mortality data from lithotomy. Surgery was risky, 1 in 7.29 cases died, even in a center with highly skilled surgeons. In the most recent years, with the adoption of the lateral lithotomy of Cheselden, the rate was reduced to 1 in 8.42 "*which differs very little from the average of CHESELDEN, whose improved lateral operation they followed*." He calculated tables of mortality that were both age and gender specific (Table 16.2) [34]. Yelloly concluded the first portion by discussing both the history of the speculative reasons why the county had such a high incidence of stone disease. He quoted the works of those who had speculated about this previously but especially the work of his former friend and mentor, Marcet. He noted that Marcet had

Table 16.2 Information from Yelloly's papers

Age or sex	Operations	Cured	Died	Mortality
Part one, mortality of surgery by gender and age				
Both sexes	649	560	89	1 in 7.29
Males	618	531	87	1–7.1
Females	31	29	2	1–15.5
Both sexes				
Under 14	292	272	20	1–14.6
14 and upwards	357	288	69	1–5.17
14–40	155	140	15	1–10.33
40 and upwards	202	148	54	1–3.74
14 to 50…	196	171	25	1–3.56
50 and upwards	161	117	44	1–3.56
Under 16…	317	294	23	1–13.78
16 and upwards	332	266	66	1–5.03
Part two, mortality of surgery by deciles of age				
Inf. to 10	255	237	18	1 in 14.16
10–14	37	35	2	1–18.5
14–20	62	55	7	1–8.85
20–30	47	42	5	1–9.4
30–40	46	43	3	1–15.33
40–50	41	31	10	1–4.1
50–60	92	69	23	1–4
60–70	63	43	20	1–3.15
70–80	6	5	1	1–6

attempted a chemical analysis of the stones from Norfolk and Norwich Hospital, but only the outer layers of the stones had been previously analyzed. The second part of this first paper would attempt to correct this shortcoming [34].

The second part of his 1829 paper was titled *Part II—Of Urinary Concretions.* In this section he presented his detailed chemical analysis of 330 of the 649 specimen stones from the collection. In his own words he stated "*Within the last four or five years, a certain portion of the calculi have been divided; and these, as well as such as were broken in the extraction, amounting together to about 330, I have carefully examined*" [34]. He used the classification of Wollaston and Marcet in reporting each type, layer by layer. Lithic acid (uric acid) was noted principally in 81, lithate of ammonia in 20, oxalate of lime in 20, phosphate of lime in 4, and fusible (mixed struvite and carbonate apatite) in 37 of the patients with a predominate single stone type ($n=162$ stones) [34]. He noted "…*that about one half of the specimens are composed of one description of material only; and that the remainder consist of alternating layers, more or less numerous of most of the substances of which human urinary calculi are composed*" [34]. He spent the final portion of this part discussing the chemistry of each of the species of minerals common to urinary calculi. He believed that the lithic acid is the most significant element in human stone disease but speculated that the oxalate stones might be important, especially in animals and noted that rats and pigs had these types of stones.

Yelloly did not waste time proceeding with his second paper *Sequel to a Paper on the Tendency to Calculous Diseases, and on the Concretions to Which Such Diseases Give Rise* [36]. He notes that he had wanted to chemically examine the entire collection of stones in the Norfolk and Norwich Hospital's collection in his first treatise and states he has been given the authority to complete this task now. Though he concludes that there were no new findings and that lithic acid again is the most predominate type of stone and the most important, he does derail his discussion to concentrate on a new found substance in some oxalate of lime stones, *silex.* He goes to unusual lengths in the chemistry of this component noting that it was also described in two oxalate stones in France by Fourcroy and Vauquelin and in Prussia by Wurzer [36]. This is a siliceous particle and it was not quantified previously by these other authors, and he notes that Michael Faraday and Dr. Prout assisted him in quantifying this substance. Yelloly goes on for the remainder of this second paper to give data on the incidence of stone disease gathered from communication with others throughout England and Ireland. He notes "*Where the circumstances which have a tendency to produce calculous diseases, are so very obscure, so difficultly traceable, and so full of anomalies, I have thought it useful to notice the local situations which are remarkable either for the frequency or unfrequency of such analogies, or discrepancies, which may not before have been sufficiently the subject of remark*" [36]. This would be certainly be a nineteenth-century attempt at clarifying the unclarifiable if ever there was an example. Yet, he goes on to ponder the possibility that stone disease is linked to a gastro-intestinal disturbance but is unsure of the type. He concludes his writings on stone disease with an appeal to surgeons as follows: "*Before closing my observations, I cannot forbear expressing my regret, that since the introduction of lithotrity by M. Civiale, as a succedaneum for the operation of lithotomy, the beneficial effects of that practice do not seem to have been completely established in this country; though it has been recommended by the singular dexterity, and the conciliating deportment, of the Baron Heurteloup and Mr. Costello*" [36].

Sir Astley Cooper

Astley Paston Cooper was born on August 23, 1768, at Brooke Hall, Norfolk, near Norwich. He was the fourth son of the Reverend Samuel Cooper who was so influential in the founding of the Norfolk and Norwich Hospital. Five of his sisters and one brother died of tuberculosis while he was a child and perhaps accounts for his devil-may-care attitude and reputation as a practical joker in his youth [37]. In his twilight years, he recounted the decisive moment that his mentor confronted him with a cadaver's arm and demanded that he dissect it. He noted from that point onwards "*that he felt the day wasted if he laid his head on his pillow without having dissected something*" [38]. After working as a youngster with the lithotomists in Norwich, he went to London for further medical training first at Guy's Hospital with his uncle William Cooper. He quickly jumped to St. Thomas's Hospital and worked with Henry Cline a pupil and apostle of John Hunter's, where Cooper too fell under the spell of the father of experimental surgery. He married Anne Cock and began to explore his more radical ideologies by traveling to Paris during "the Terror" in 1792 [37]. His meteoric rise resumed on his return to London, and by 1800 he was the senior surgeon at Guy's Hospital [39]. He was in many aspects similar to his idol, John Hunter, except in his clinical surgical practice where his indomitable personality allowed him to push the envelope of surgery in virtually every direction. Cooper sought out disease and patients in which to try out new ideas. He operated upon people with little warning and sometimes without their consent. He even was known to have operated upon patients who refused consent. "*Sir,*" protested one of his patients afterwards, "*you had no right to do that without consulting me; God bless my soul! Sir, the pain is intolerable;—if you had asked me, I don't think I should have submitted*" [40]. He was literally the aggressive surgeon that has been caricatured in modern times, when a surgery was indicated then it should be done. Astley Cooper was a dynamic and engaging surgeon who developed many relationships with colleagues, students, physicians, and aristocracy. He was called to treat the infected cysts of King George IV and received a baronetcy in 1820. Cooper celebrated by providing a dinner for all members of the Pow Wow Club (a favorite of John Hunter's), which John Yelloly was a member [40]. Finally, Cooper profoundly influenced another young student who was torn over the horrors of medicine and surgery and the ethereal qualities of poetry, John Keats [41].

Because of the risks of lateral lithotomy, especially in older males with larger prostates, Cooper introduced some unique modifications. Instead of widening the prostatic urethra with a knife, he tried to dilate this with a fluid dilator containing mucilage. He called this *lithectasy* or *cystectasy* when he tried this in 1819. But even in Cooper's hands this took over forty hours and never became popular [42]. He presented unique instruments for special types of stone cases. In 1821 he wrote a paper on a special transurethral forceps for removal of numerous small bladder stones for patients with enlarged prostates [43]. In this article he discusses multiple cases in elderly men who passed numerous small stones and his innovative device for extracting multiple small stones. In another paper the following year, Cooper wrote about removing even large bladder stones by dilation of the female urethra with an innovative dilating device [44].

A final anecdote of Astley Cooper will complete this portion from his Norwich/Norfolk origins. At about 1 P.M. on Tuesday, March 18, 1828, a previously healthy patient by the name of Stephen Pollard presented himself to the operating table at Guy's Hospital [45]. Pollard was a family man with a wife and five children from Sussex, and at age 53 he was suffering from a bladder stone. Bladder stones are painful, and patients often presented themselves to the mercy of surgeons with the obvious dilemma of continued pain versus the exquisite agony of the surgical procedure itself. Most lithotomies were over in minutes, in fact, until the case of Pollard's no stone surgery at Guy's Hospital had lasted for more than 30 min. But a young surgeon, Bransby Cooper who was Sir Astley Cooper's nephew, was doing this case. Bransby Cooper panicked during this routine surgery and is believed to have injured the rectum in the process. The surgery lasted an agonizing 55 min in front of 200 spectators. A friend of Sir Astley Cooper and editor of the new medical journal, The Lancet, railed at the ineptitude of the young surgeon in print. Supposedly the increasing horror of the frantic surgeon caused even the seasoned surgeons in the crowd to leave the hall. Mr. Pollard cried out in agony "*Oh! Let it go! Pray, let it keep in!*" Cooper called out to those remaining in the crowd that "*It's a very deep perineum. I can't reach the bladder with my finger.*" He called for his assistant to raise his hand to see if his fingers were longer. He finally found the bladder and removed the culprit. This token of endurance resides rather inconspicuously in the Gordon Museum at Guy's Hospital, about 3 cm across. Pollard died the following morning and an autopsy was performed. This revealed that he sadly did not have a deep perineum and Thomas Wakley reported to enraptured readers of the Lancet that in issues 239 and 240 he recounted the disastrous surgery from eye witness accounts. One headline read "*Guy's Hospital. The operation of lithotomy by Mr. Bransby Cooper which lasted nearly one hour!*" Bransby Cooper sued the Lancet for libel and sought £2,000 [46]. The trial made headline news about the quality and standards for practicing complex surgery (Fig. 16.3). Astley Cooper, who was called to give evidence regarding his nephew, stated "*I think he is already a very good surgeon, but I do not think he is a perfectly good surgeon. Give him time. Do not crush him at the outset of his career.*" The jury in 1828 awarded the suit to Bransby Cooper, but only for £100. It is fitting that Dr. Thomas Wakley had raised funds for his defense that exceeded this amount which he gave to the widow Pollard and her children.

Fig. 16.3 "The lancing of Cooper," during the furious trial of 1828 regarding Sir Astley Cooper's nephew and the famous case of lithotomy at Guy's Hospital

Dr. Civiale

Jean Civiale (1792–1867) became a world-renowned surgeon shortly following his medical schooling. Civiale was born in Salilhes (Cantal) and died in Paris. He began to study medicine late in life and was still a student in Paris when he presented to the Institute his first essays on lithotripsy through the urethra without an incision. He was associated with the great surgeon, Dupuytren, and he began considering less invasive methods to trap and hold bladder stones. It is recorded that he would walk around the hospital and Paris with his lithotrite in his pocket and practice constantly grabbing objects in his pocket blindly anticipating his future efforts on bladder stone patients [47]. Civiale had become interested in the dissolution of stones but was keenly aware of the problems of varying stone types and generalized ineffectiveness of this method. In addition, several workers tried transurethral entrapment of stones in pouches so as to deliver much more toxic substances in order to facilitate chemical destruction without injuring the bladder. Surgeons had even tried to develop instruments to sample a portion of the stone to better decide if dissolution was possible. He performed his first lithotrity on a living patient on January 13, 1824, with a crowd of spectators watching; he was flawless. He utilized his own instrument which he designed called the *lithontripteur*. He noted that his instrument was a modification of Alfonso Ferri's *alphonsinim* [47]. He could not only grasp the stone by a three-pronged pincer but could also crush it while being held. His instrument was a trilabe, a three-bladed forceps for holding a stone. A sharp-pointed drill cut away at the stone and the fragments could be washed out of the bladder [29]. Overall, the original apparatus was only effective on soft stones, but he did persist and developed stronger instruments, but so too others had entered the field of lithotrity as well, improving the instruments along the way [48].

There was always controversy on who is the first; Leroy d'Etiolles (1798–1860) appears to have designed a similar, if not identical, lithotripter to that of Civiale. These were both excellent stone fragmenting devices and were rapidly replaced with even better instruments. A stone gripping and grinding device was developed by Heurteloup in 1832. The hammer was added as an adjunct for difficult stones and a stone-crushing screw was developed by Pierre Salomon Ségalas (1792–1875). Though Heurteloup, Amussat, Leroy d'Etiolles, and Civiale argued about primacy, the Académie des Sciences awarded credit initially to Leroy in 1831 but reversed this decision in 1833 favoring Civiale [48]. If in fact true lineage is sought, Cooper's use of his modified extractor was in fact also a lithotriptor which was designed and made for him by John Weiss [43]. In 1826 the Acadédmie des Sciences awarded Civiale a prize for his lithotrity. The following year he received the prestigious *Prix Montyon* award. The Parisian Hospital administration allocated Civiale several beds in the Necker Hospital, thereby creating the first unit for stone disease in Paris by 1824. Regardless, Civiale created the first urology department at the Necker Hospital. Civiale wrote numerous essays: *Nouvelles considerations sur la retention d'urine* (Paris, 1823), *De la lithotritie ou broiement de la pierre dans la vessie* (Paris, 1827), *De l'uréthrotomie* (Paris, 1849), *Traité pratique et historique de la lithotritie* (Paris, 1847), and *Traité des maladies des vlies urinaires* (Paris, 1850) [47].

As mentioned previously in the section on the Norwich School of Lithotomy, Civiale was keenly aware of the records kept at this institution and tried to replicate this information throughout Europe. He was aware of the study by Matthew Dobson (1799), Alexander Marcet's work of 1817, and John Yelloly's from 1828 to 1829. He utilized the sponsorship from the Ministry of Public Instruction to gather information on stone disease and lithotomy. In 1835 he produced the first European large-scale statistical data which he immediately utilized to compare his new technique to the standard lateral perineal lithotomy. In this presentation to the Académie des Sciences, he compares his series of 257 patients to 5,715 lithotomies. His data showed that 6 or 2.3 % undergoing lithotrity died versus 1,141 or 20 % for lithotomy. The French National Science Academy urged by factions immediately responded with their own statistical inquiries also published in that year [49]. It is interesting to note that the reporter Francois-Joseph Double (1777–1842) was a well-known physician and one of Napoleon's surgeons. Dominique-Jean Larrey (1766–1842) was a physician-chemist also interested in stone disease. These physicians and mathematicians were skeptical about the applied mathematics to medicine, though synchronous to these studies, Pierre Charles Alexandre Louis (1787–1872) was pioneering statistics in studies on phthisis (1825) and typhoid fever (1828) and coined the term *method numérique* that profoundly changed all of medicine [50]. Indeed it would be Louis and his method that would finally prove that bleeding had no beneficial effect, and it would quietly vanish for treatment of stone disease as well [50].

The Necker Hospital and Paris

Madame Suzanne Necker (1739–1794) founded the hospice in 1778 with 102 beds; this later became the Necker Hospital in 1802 [51]. It is here that Civiale was given room and access to patients. Civiale died in 1867 and the opening at the Necker needed someone to fill this void. Jean Casimir Félix Guyon (1831–1920) was the first surgeon to hold a Chair in Urology thus making him known as the "father of Urology." It is fitting he followed Civiale at the Necker Hospital. He was born on July 21, 1831, on Bourbon Island (Reunion) into a medical family. He studied in Nantes and transferred to Paris passing his exams in 1853 at age 22. In 1863 he defended his *these d'internat* entitled "*The abnormalities of the urethra*." He became increasingly interested in uropathology, and the Bureau Central des Hôpitaux advised him to take the position vacated at Necker [52]. A long lineage of urologic greats followed in succession. Guyon was Professor and Chief of Urinary Tract Diseases from 1867 to 1906. Joaquin Maria Albarran (1860–1912) followed as Professor of Clinical Urinary Tract Diseases and Chief of Necker 1909–1912. Felix Legueu (1863–1939) in turn became Professor of Urology and Chief of Necker 1912–1933, followed by Georges Marion (1869–1960) and Roger Couvelaire (1903–1986). These individuals trained and developed interests in a whole range of urinary tract diseases that began with bladder stones and a vision of Jean Civiale to utilize advanced tools to minimize morbidity and mortality. In 1847 a young British surgeon repaid the visit to Cheselden by Morand; his name was Henry Thompson (1820–1904). He learned lithotrity from Civiale and later was elected to the Sociéte de la Chirurgie as well as becoming the surgeon of royalty. The Necker Hospital became the leading institutions for these rapid advancements, the patient at home with even a surgeon such as Sir Astley Cooper was rapidly changing.

St. Peter's Hospital for the Stone

Specialty hospitals have a long and complex history. Along with the potential to rapidly advance investigation and treatment for specific disease entities, such specialty-specific institutions rather incite a firestorm of negative dialogue by generalists who feel that it detracts from the general capacities of community hospitals. St. Peter's Hospital for Stone was founded on the cusp of the American Civil War in 1860. This is somewhat late in the history of specialty care in London with psychiatric, women's, pediatric, ENT, chest, and cancer institutions already having been built and in service by this time. History of St. Peter's started with an appeal for public support on March 12, 1860, stating "*Some Noblemen and Gentlemen now propose to supply the existing want by founding an Hospital for the treatment of Patients laboring under Stone and other diseases of the urinary organs*." The Registrar-General also had noted that the number of deaths from stone and other diseases of the urinary organs had markedly increased in England, having doubled from 1850 to 1860 [53]. The Hospital for Stone opened its doors in the autumn of 1860 at 42 Great Marylebone Street. It was initially small, little more than a few beds, but in 3 years' time it was deemed time to move to large accommodations at 54 Berners Street in 1863, now 15 beds. The name now changed to St. Peter's Hospital for Stone. Mr. W.J. Coulson held the appointment of surgeon which he held for 25 years [53]. There were many critics to the specialty Stone Hospital, and many articles were written in the British Medical Journal during these early years. On February 1, 1873, a mysterious benefactor changed all of the financial problems for the institution when he anonymously delivered an envelope containing 10 thousand pound Bank of England notes with no stipulations on to the spending or allocation of this gift [53]. The British Medical Journal promptly reported this philanthropy as the Hospital again relocated to Henrietta Street, Covent Garden, in 1882. The new St. Peter's Hospital for Stone was officially opened by the

His Royal Highness Prince Leopold, Duke of Albany, on June 29, 1882. The mortality from stone surgery has been reported in the decade between 1864 and 1873 following lithotrity of Civiale was 15.25 % and the average hospital stay was 100 days. In the decade 1915–1924, the litholapaxy method of Bigelow had been introduced and the mortality rate fell to 2.2 % with the average hospital stay down to 5 days [53].

St. Paul's Hospital was founded by Mr. Felix Vinrace who influenced a group of Londoners who met on May 27, 1897, "*to consider the desirability of founding a hospital in Central London for the treatment of the many forms of skin and cognate diseases so prevalent in our midst.*" The site for the new hospital was 13a Red Lion Square, and they proposed an inscription "*For Skin and Genito-Urinary Diseases*" [54]. This caused quite a stir among the locals as being indecent. The hospital was proposed to be the most modern facility "*replete with every accommodation befitting a modern hospital, embracing, obviously, its lighting throughout by electricity*." St. Paul's opened its doors to the needy on August 15, 1898, with Mr. Vinrace, M.D., F.R.C.S., as the senior honorary surgeon with six inpatient beds. In the first year there were 1,142 new cases and 7,100 attendances. There were also 16 surgeries in the first year with no fatalities. By 1904 there were four surgical staff and two anesthetists. In 1913 treatment with "606" was first tried and X-rays were installed. World War I made the treatment of venereal diseases a new incentive, and St. Paul's was flooded with 20,000 outpatient attendances. The hospital needed more space but finances were lacking. Finally in 1923 the hospital was relocated to what was the British Lying-in Hospital at Endell Street. St. Paul's installed a cystoscopy suite as early as 1926 and added X-ray capability to it the following year. The wards also opened with 18 beds for inpatients. St. Peter's and St. Paul's finally amalgamated their similar interests on May 9, 1948, to become the Institute of Urology [54].

John Swift Joly (1876–1944) was born in Athlone, and his father was also a minister of the same name. He studied medicine at Trinity College, Dublin, graduating in 1902. He went to the European centers to learn the latest in surgery prior to returning to London where he worked with Sir John Thompson-Walker at St. Peter's Hospital for Stone. He later became the senior surgeon as well as the consulting urologist for the Navy during World War I. He was particularly interested in stone disease and wrote the influential "Stone and Calculous Diseases of the Urinary Organs" in 1929 [29].

Another St. Peter's Hospital for Stone great was Winsbury-White. Horace Powell Winsbury-White (1889–1962) was born in New Zealand on September 28, 1889. He was educated at Marlborough College, New Zealand, prior to attending Edinburgh University graduating in 1914. He was Resident Surgical Officer at St. Peter's Hospital for Stone and continued at the three P's (St. Peter's, St. Paul's, and St. Phillip's Hospitals). He is the cofounder of the British Journal of Urology in 1929 and its first editor, now the British Journal of Urology International (BJUI) that has been published for just over 80 years [55]. He too wrote a textbook on stone disease that has survived as a classic [56]. It would appear that the original mandate in 1860 has achieved its stated purpose and promise not only to London but also to the world. The knowledge of stone disease certainly has been advanced due to the efforts of individuals from St. Peter's Hospital for Stone. The mysterious benefactor also might never be known, but that donation certainly has paid substantial dividends.

Conclusions

John Keats has been literally evaluated into minutia by recent academic explorations of his poetry in context to the general culture of medicine upon which this chapter has focused [57]. John Keats was born at the "Swan and Hoop," Moorgate Pavement, on October 31, 1795. His father died when the boy was but 8, and he was sent to school at Enfield where the Clarke's seemed to have adopted him. He excelled at school with an affinity for Latin and Greek, winning several student awards. He also loved the pugilistic arts, boxing. At age 15 he was moved from the school to apprenticeship with Mr. Hammond a surgeon and apothecary in Edmonton. Little is known of Keats in his apprentice days; however, one student noted "he was an idle, loafing fellow, always writing poetry" [58]. We do know that a friend Cowden Clarke managed to arrange 1 day release for Keats to return to school for lessons. In 1814 during his indenture, a quarrel between master and pupil resulted in a broken contract by mutual consent. Keats went to the United Hospitals of Guy's and St. Thomas where he stayed between 1815 and 1816. He attended anatomy and surgery lectures by Henry Cline and Astley Cooper. The lectures in medicine were given by Dr. Babington and Dr. Curry. He went to lectures on chemistry and the chemistry of stone disease given by Alexander Marcet (one of the founding fathers). His lectures in midwifery were given by Dr. Haighton [59]. In need of cash he became a dresser and his chief was Mr. William Lucas, Jr., but Keats was attracted to Cooper's surgical room [59]. It is during this time that Sir Astley Cooper took special interest in Keats, and Keats became a brief lifelong admirer of Cooper. Cooper in fact arranged lodgings for Keats in St. Thomas's Street. On May 5, 1816, Keats had his first poem published in *The Examiner* that was a sonnet called *Solitude* [60]. He was only 21 and attending school at the United Hospitals of Guy's and St. Thomas's! Two of his subsequent poems *Endymion* and *Hyperion* appear to be strongly influenced by his student year. Medical school examinations again intruded upon his poetry, and he sat his exams in Apothecaries Hall at Blackfriars on July 25, 1816, which he passed [58]. He continued to work as a dresser until the winter of 1816, but he longed to devote himself to his writing [59].

Keats's first published volume of poetry was issued in 1817 and contained a piece he was working on while at Guy's, *On First Looking into Chapman's Homer* [60]. The next 4 years he led "*a fitful life, here and there, no anchor*" [58]. In 1818 appeared *Endymion.* His own preface revealed that he believed his powers to be not at their fullest [60]. In June of 1820 he published his third volume, *Lamia, Isabella, The Eve of St. Agnes, and other poems* [60]. Keats was now lauded by all, and on the eve of greatness, he began having bouts of hemoptysis eventually leading to his tragic death at age 25 [58]. It was here at the door of tragedy he displayed a warmth of character by playing a practical joke on a friend named Brown who had leased his house to Nathan Benjamin. The water for this domicile came from a tank lined with lime imparting an unpleasant taste. Keats wrote a note to Brown:

> *Sir,- By drinking your damn'd tank water I have got the gravel. What reparation can you make to me and my family?*
>
> Nathan Benjamin

An answer was soon forthcoming:

> *Sir,- I cannot offer you any remuneration until your gravel shall have formed itself into a stone, when I will cut you with pleasure.*
>
> C. Brown [58].

Sir Astley Cooper would most certainly have approved of the jocularity and the surgical implications. Nowadays, centers have again begun the slow process of specialization that markedly influences outcomes. We will return to this concept in the final chapter of this book. But the historical sojourn to this point, alluded to in the previous section regarding St. Peter's Hospital for Stone, clearly points to the fact that a single individual, not necessarily an institution, does the yeoman's work in caring for individual patients. It is a fitting ending and a tribute to those who suffered and survived, to those who agonized and perished, and to those subject to the knife, while those wielding this merciless instrument of steel were also struggling to learn the "craft" upon the unwitting likes of Stephen Pollard. John Keats wished to be buried with an epitaph on his tombstone, "*Here lies one whose name was writ in water*." This in turn was utilized by his friend Percy Bysshe Shelley, died and buried in the same graveyard in Rome and found at death with a copy of Keats's latest book in his back pocket, so hauntingly appropriate to stone patients from a little known Shelley verse.

> *Here lieth one whose name was writ on water.*
> *But, ere the breath that could erase it blew,*

Death, in remorse for that fell slaughter,
Death, the immortalizing winter, flew
Athwart the stream,- and time's printless torrent grew
A scroll of crystal, blazoning the name
Of Adonais…
Shelley, *Fragment on Keats* [61]

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17 Liesegang Rings

Introduction

> "*Crystals and Configurations are frequently seen together in the same Drop, and forming at the same Instant. As soon as the Crystals become discernable by the Microscope, they are either Cubes, or Rhomboids, or Columns, or pyramidal, or triangular, or some other certain Figure; and to what Bigness soever they may become inlarged, they shew, from their very first Appearance, the same Sides and Angles that are seen afterwards when at their utmost Size, no Alteration of Figure attending their increase in Bulk.*"
>
> Henry Baker, 1753 [1]

Stones are in fact mineral structures and from mankind's earliest recorded times; minerals have had some degree of interest, even to the Ancients. Gemstones in particular have always been sought and coveted. Babylonian, Greco-Roman, Chinese, and Sanskrit texts all presented studies of minerals. Both Aristotle and Theophrastus discussed minerals and some of their properties. Aristotle did so in his *Meteorologica*. Aristotle theorized that all minerals are combinations of the four basic substances: water, air, earth, and fire. Theophrastus expanded upon this theme in his *De Mineralibus*; he essentially makes two large categories, those affected by heat and those by water [2]. But we must move to Pliny the Elder's 23 CE to 79 CE (current era or AD) work just prior to his volcanic extinction called *Naturalis Historia* for a near modern description of minerals. Pliny spent five entire volumes on minerals, classifying them as "*earths*, *metals*, *stones*, *and gems*." He discussed not only the properties of minerals he also discusses their applications and uses. He also might be the very first investigator to mention crystals. He noted that diamond had a natural "octahedral shape." He also discusses mining in some detail [3].

In the later part of the Renaissance, mining became a substantial industry, especially in what is now Southern Germany and the science of mining became established. Georg Bauer, Latinized to Georgius Agricola, wrote his magnum opus in 1530, *Bermannus*, *sive de re metallica dialogus*. Many believe that this book is the beginning of the science of mineralogy making Georgius the father of mineralogy. He was also the town physician of Joachimsthal, one of the centers of mining. Similar to Paracelsus, Agricola was critical to the knowledge of the Greco-Roman and Middle Eastern ancient writers. He subsequently published *De veteribus et novis metallis* in 1546. And his best-known work followed, *De re metallica*, in 1556. He did praise Pliny for his pioneering discussions about minerals and mining [4]. He began to speculate on the reasons for ore channel and the work of ground waters. He questioned all information and suggested methods of investigation. His work was carried on by others including Anselmus de Boodt (1550–1632) of Bruges who wrote *Gemmarum et Lapidum Historia*. A German mining chemist named J.F. Henckel followed with his *Flora Saturnisans* in 1760 [5].

Crystals are the building blocks of stones as well as snowflakes (Fig. 17.1a). The crystal is the unit that accumulates with known principles of chemistry and physics. That stones grow with

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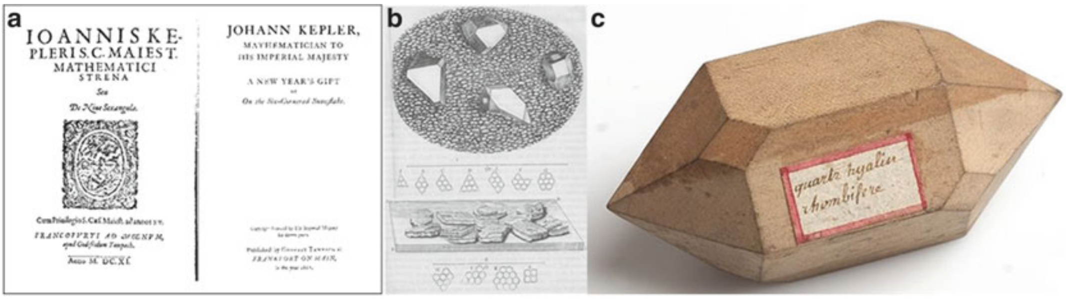

Fig. 17.1 (**a**) Crystals from snowflakes (Kepler, 1611), (**b**) Robert Hooke's *Micrographia* (1664), and (**c**) René Just Haüy's crystals from *Traité de Cristallographie* (1822) (pear wood models)

some degree of regularity is readily apparent by simply slicing stones, which have been done for centuries. A periodic process is apparent in human kidney stones, in tree trunks, in growing corals, in sea shells, and even in ice deposition in the Arctic and Antarctic. All throughout nature, these periodic precipitation patterns were apparent and have been systematically investigated for over 100 years. But the crystals themselves have a quite fascinating history. This includes the father of science itself, who became the leader of a small band of intellectuals who called themselves the "*Philosophical Breakfast Club*" [6]. The story includes the enigmatic scientist who left his fortune to found the Smithsonian Institution, James Smithson. The crystallographers often were mineralogists, chemists, and physicists but most importantly they were also collectors of rocks.

Crystals

In the mid-thirteenth century, the theologian John Duns Scotus believed that crystals lived and grew much like plants. He thought that their structure represented a pure form or an ideal shape that harkened back to Plato [7]. The German astronomer and mathematician Johannes Kepler (1571–1630) wrote a short treatise "The Six-cornered Snowflake" in 1611 and first proposed that these were derived from tiny, spherical elementary particles [8]. Nicolas Steno (1638–1686 or his Danish name, Niels Stensen) was a brilliant physician and polymath who was interested in many scientific subjects. He was briefly a professor of anatomy at Padua in 1666 before coming to the Palazzo Vecchio under the Medicis where he interacted with Francesco Redi and was introduced to Marcello Malpighi [9]. He argued that the growth of minerals was due to the accumulation of particles precipitated from liquids. He believed that an "*outer force*" produced the growth of crystals. He noted that the angles of crystals' regular faces were always the same in his work *Prodromus* in 1669 [10]. Sir William Osler once noted of Steno, "*No one should have a warmer place in our memory than the anatomist, geologist and theologian, whose name is on our lips in connection with the duct of the parotid gland…A strange figure, one of the strangest in our history…*" [11]. Much of Steno's work on minerals, fossils, and geology were introduced to the Royal Society by Martin Lister and William Croone who he met while visiting the medical school at Montpellier [12].

Robert Hooke (1635–1703) has been described as the Leonardo of London because of prolific investigations and writings in so many areas of learning [13]. Hooke in his 1665 book *Micrographia* described the "*fantastical*" (structural, not pigment) colors of the peacock's feathers, "*The parts of the Feathers of this glorious Bird appear, through the Microscope, no less gaudy then do the whole Feathers; for, as to the naked eye 'tis evident that the stem or quill of each Feather in the tail sends out multitudes of Lateral branches, … so each of those threads in the Microscope appears a large long body, consisting of a multitude of bright reflecting parts. … their upper sides seem to me to consist of a* *multitude of thin plated bodies, which are exceeding thin, and lie very close together, and thereby, like mother of Pearl shells, do not only reflect a very brisk light, but tinge that light in a most curious manner; and by means of various positions, in respect of the light, they reflect back now one colour, and then another, and those most vividly. Now, that these colours are onely fantastical ones, that is, such as arise immediately from the refractions of the light, I found by this, that water wetting these colour'd parts, destroy'd their colours, which seem'd to proceed from the alteration of the reflection and refraction*" [14]. He would go on to discuss his concept of crystals forming from spherical particles (Fig. 17.1b).

In his book Micrographia he approaches his section on crystals by first discussing human urine in his *Observation XII. Of Gravel in Urine*. He begins "*I Have often observ'd the Sand or Gravel of Urine…through the Microscope, appear to be a company of small bodies, partly transparent and partly opacious, some White, some Yellow, some Red, others of more brown and duskie colours. The Figure of them is for the most part flat, in the manner of Slats or such like plated Stones…*" [14]. He continues with the now age-old wish "*How great an advantage it would be to such as are troubled with the Stone, to find some menstruum might dissolve them without hurting the Bladder, is easily imagin'd since some injections made of such bodies might likewise dissolve the stone, which seems much of the same nature*" [14]. Now he proceeds with *Observation XIII. Of the Diamants, or Sparks in Flints*. Here he presents his work that so stunned Wollaston, a work on the microscopic structure of "*Crystaline or Adamantine bodies, so curiously shap'd, that it afforded a not unpleasing object*" [14]. He had moved on to investigate a crystalline stone commonly called Cornish diamonds. He begins to question the formation of the crystals and speculates on why they form "*triangular, trapexoidal, rhoboeid, hex-angular, tetrahedron forms*" [14]. He comes to his theory that floored Wollaston, "*I could make probable, that all these regular Figures that are so conspicuously various and curious, and do so adorn and buautifie such multitudes of bodies, as I have above hinted, arise onely from three or four several positions or postures of Globular particles, and those the most plain, obvious, and necessary conjunctions of such figur'd particles that are possible, so that supposing such and such plain and obvious causes concurring the coagulating particles must necessarily compose a body of such a determinate regular Figure, and no other, and this with as much necessity and obviousness as a fluid body encompast with a Heterogeneous fluid must be protruded into a Spherule or Globe*" [14]. Hooke like Boyle, Dalton, Kepler, Huygens, and Wollaston all have developed a picture that is rather modern molecular stoichiometry.

Crystallization

Henry Baker (1698–1774) was predominately a writer but was interested in science, history, and poetry; he translated Molière and was an editor. He became enamored with the microscope based upon Hooke's influential book and the reports from Antonie van Leeuwenhoek [15]. He is mostly remembered today for being one of the early popularizers of microscopy with his 1742 book *The Microscope Made Easy* [16]. This became a best seller and vaulted Baker into a fellowship of the Royal Society. He followed this work with the much more intriguing secondary investigations that focused upon salts and crystals. This was published in 1753 and was entitled *Employment for the Microscope in Two Parts* [17]. The book has 32 chapters on a variety of microscopic investigations, but it is the seven chapters that deal specifically with different crystals that deserve some attention. Baker appears to have been aware of Moritz Anton Cappeler's (1685–1769) 1723 coining of the word "crystallography." Baker also notes on page 7 of his text that discussing crystals is one thing, trying to demonstrate their three-dimensional complexity was quite another. He notes "*Drawings therefore have been made, and Copper Plates engraven, at no small Expense, of the different Configurations hereafter mentioned: which, though greatly deficient in Beauty and Regularity, if compared with* *the Originals*, *and only pretending to give such a general Resemblance as may distinguish each Kind from other*…" [17]. This problem would be solved using three-dimensional models that were used in Paris.

One of the first great French crystallographers was Jean-Baptiste Louis de Romé de L'Isle (1736–1790) who collected minerals and employed a goniometer to study crystal angles. He was also the first scientist to make models of crystals that were larger and easier to study, some made of porcelain from the Royal Porcelain Manufacture of Sèvres and others made of brass. In 1783 de L'Isle published his *Cristallographie* in Paris that contained hundreds of mineral discriptions [18]. René Just Haüy (1743–1822) was a French priest and scientist who studied crystal growth, crystal geometry, and the concept of unit cell. He may well have known about some studies done on the regular cleavage of calcite by the Swedish mineralogist Torbern Bergman in 1773. In 1784, Haüy presented his work on the constancy of interfacial angles. He suggested that crystals were made up of elementary building blocks which he called "*integral molecules*" which were quite distinct from the ideas of Kepler, Hooke, and Huygens who all believed in the notion of atoms [19]. He called the macroscopic structure as a three-dimensional periodic array of the integral molecules. Haüy concluded that fragments of crystal cleavage resulted from three molecular forms: the tetrahedron, the triangular prism, and the parallelepiped. He also developed a series of wooden crystal models because of the three-dimensional illustration of these complex entities. Haüy also came up with the marketing idea of including a set of the three-dimensional models to help promote the sales of his textbooks, which succeeded (Fig. 17.1c). He also published works in 1801 and 1815 furthering his studies of crystals. Though controversial, no one could argue against these findings until better instruments were developed. This would not take long, as Wollaston followed in 1809 with his instrument that was refined but still used today. Haüy's theories attracted controversy, initially by Romé de L'Isle who called him a "cristalloclast" (crystal smasher) but also a German investigator named Weiss. Haüy simply ignored most of his detractors and continued to work and publish. His magnum opus was published in 1801 called *Traité de Minéralogie* followed by his *Traité de Cristallographie* in 1822 [20, 21].

Louis Pasteur was born in the small town of Dôle late that same year on December 27, 1822, and became one of the truly monumental contributors to medicine though he was not a physician [22]. He attended the famous Ecole normale supérieure in Paris (where Haüy taught) and followed a pathway into science. In 1847 he began to prepare for his doctor's degree at age 24, and he became intrigued with crystallography. He had read some of the work of Mitscherlich in Germany on peculiar characteristics of crystals of tartaric acid. One of his teachers at the Ecole normale, Delafosse, had also noted right- and left-handed facets to quartz crystals when rotated in polarized light. Using tartaric acid Pasteur was able to successfully identify racemic crystals after just 2 years in the laboratory at age 25: "*I have just made a great discovery*…*I am so happy that I am shaking all over and am unable to set my eyes again to the polarimeter*" [23]! This was just the beginning for this gifted young man [24].

We've already discussed William Hyde Wollaston (1766–1828, one of the founders of stone chemistry) in several places in this history of urolithiasis, but we shall now concentrate on his contributions to understanding crystals, crystallization, crystal physics, and the chemistry of stone disease in more detail. Wollaston came from a rather incredible background. His grandfather was interested in science and theology and wrote "*Religion of Nature Delineated*" in 1724. His father named Francis Wollaston was a vicar and fellow of the Royal Society. He was interested in astronomy and wrote "*Fasciculus astronomicus*," a star catalogue in 1800. His uncle was perhaps more famous than all of the rest; he was William Heberden (1710–1801), a physician/scientist who is considered a giant in medical history as well as a member of the Royal Society. Another uncle, Charlton Wollaston, was a royal physician to the Queen, a fellow of the Royal Society, and a Harveian orator in 1763. His older brother Francis also attended Caius College, Cambridge, and was a lecturer in mathematics and later became the Jacksonian professor of chemistry. His intimate friends included his pupil and protégé, Alexander Marcet. Sir Humphry Davy was also considered a friend and they died within months of each other. He knew and interacted with possibly the most gifted intellectual of the age, Thomas Young, and they investigated many of the same problems and both served on the Board of Longitude [25]. Wollaston was so highly thought of in his own time that a French mineralogist named wollastonite in his honor. Wollaston Island was named for him by the Arctic explorer Ross.

Wollaston attended Caius College as a medical student and was interested in botany and chemistry graduating in 1787. He moved to London to complete his medical training. He practiced until 1800 when he became a full-time scientist. This might be because he was denied a position at St. George's Hospital [26]. His scientific accomplishments were amazing. He became a fellow of the Royal Society in 1793. He was awarded the Copley Medal in 1802. Between 1800 and 1803 he isolated a secret method to purify platinum which created great scientific controversy amongst those who wanted academic openness. Wollaston greatly added to his wealth with the platinum processing technique; some estimates noted his profits were as much as £15,000 by 1826. He also discovered palladium in 1802 which prompted his French counterpart, Vauquelin, to declare of Wollaston's achievement as "*seams at first incredible*." He also discovered the element rhodium in 1804.

We have previously discussed Wollaston's work in chemistry that prompted his support of Dalton's atomic theory. In 1808 Wollaston had been performing chemical experiments that brought him to urinary calculi. He already discovered that carbonate, sulfate, and oxalates were regulated by the law of multiple proportions. He even anticipated spatial considerations of stereochemistry long before this was a science. On November 26, 1812, he read the Bakerian Lecture "*On the Elementary Particles of Certain Crystals*" [27]. In this truly astonishing work, he boldly stated that the ultimate existence of physical atoms was not established and that virtual special particles, consisting of mathematical points surrounded by forces of attraction and repulsion, would explain the structure of crystals equally well. He is so close to Rutherford's atomic model. He may have been attracted to crystallography via the writings of Haüy who had created a system based upon mathematical idealism that would have appealed to Wollaston.

Wollaston invented the reflective goniometer in 1809 and began a systematic investigation of crystals and crystalline structure. Wollaston's new device gained accuracy to the nearest 5 min of arc, which was almost six times greater than Haüy's measurements. Wollaston proposed in 1812 that alternative spherical units were joined together in space into geometrical arrangements. He was stunned to find his theory in Robert Hooke's *Micrographia* as the thirteenth observation. William Phillips was a printer and bookseller who also became interested in crystallography. Wollaston taught him his methods and how to use his goniometer and he took over much of the work of measuring and recording crystalline angles [28]. He improved upon Wollaston's original measurements to an accuracy of 0.5 min of arc. This information would be useful to allow Mohs and Mitscherlich to discredit much of Haüy's earlier misconceptions. One final comment is necessary on the brilliance of William Hyde Wollaston. He died of a brain tumor and spent his last days trying to communicate his level of awareness to his close friend and fellow crystallographer James Louis Macie who later changed his last name to Smithson (more on him later). It is typical of this great mind "*to convert his death into a grand philosophical experiment, to give data for determining the influence of the body on the mind, and to try whether it was possible for the latter to remain until the very last*" [29].

Finally in the history of crystallography, we have to return to Haüy and the controversy regarding his theories. Eilhard Mitscherlich (1794–1863) was at first a classics scholar who became a physician and then for a scientist discovered chemistry and crystals. He translated much of Haüy's writings into German. In 1819 he discovered the phenomenon of isomorphism where different chemical substances have the same crystalline shape. This was at odds with the observations of Haüy's and the two would battle for the rest of the latter's life [30]. Not only that, but Mitscherlich also discovered that the same molecule called also form into different crystals, called polymorphism using calcite and aragonite ($CaCO_3$). It is Mitscherlich who brought crystallography back into the mainstream of chemistry and supported Dalton's atomic theory with the support of Jöns Jacob Berzelius (1777–1848) [31].

A major advance in crystallography occurred in 1845 when the French physicist August Bravai successfully predicted that 14 possible basic geometric atomic configurations were possible in various crystals (now called Bravais lattices). All of these speculations about structures of crystals were merely hypothetical until Max von Laue and coworkers in Munich irradiated crystals and observed diffraction patterns that correlated with the lattice structures, proving molecular arrangement of the atoms themselves in 1912 [31]. He won the Nobel Prize in physics in 1914 for his work on crystals. In 1914 the physicists William Henry and William Lawrence Bragg published the first detailed atomic arrangement of crystals. They too won the Nobel Prize in 1915 for the physics of crystals. The first textbook on crystallography to include this information was Paul Niggli in 1920 [32].

What's In a Name?

Minerals have been given all types of names, and the development of the nomenclature of these substances has a long history itself. Attempts to codify or come up with rules of naming minerals struggled until after World War II. Also, one might think that new minerals would be getting fairly rare; this too is a falsehood. Modern synthetic chemistry is racing forwards making new mineral species that have unusual properties that are exploited in engineering and manufacturing. In the eighteenth century, none other than our botanizing physician Carl von Linné (Linnaeus) tried to develop a codified method of naming minerals using his binomial Latin names. In his youth, he was actively engaged in the pursuit of geology and geological phenomena. In 1729 he made his first excursion into the mines at Dannemora in northern Uppland. In 1733 he visited the Bergslagen region again to inspect mines and investigate smelting of ores. His most profound works were in paleontology where he named several fossils species which are stilled used today. He also investigated stratigraphic geology much like Steno. Because of his influence in biologic sciences, this binomial method of naming was used for a short period of time but was dropped because of the cumbersome nature and the long antecedent history of naming already existent [33]. A.G. Werner, a German mining geologist, proposed the first chemical classification of minerals in 1774. The Swedish chemist J.J. Berzelius modified and improved upon the nomenclature, and the basis for modern crystal science was utilized in the first textbooks on this subject by Haüy (1801), Dana (1837), Breithaupt (1849), and Groth (1904).

James Smithson was the oldest son of Elizabeth Hungerford Keate Macie and for 35 years he kept his maternal last name. In fact, he was the illegitimate son of the late first Duke of Northumberland, Hugh Smithson, and there is no record of his birth in 1764 or 1765. Smithson was a brilliant student and entered Oxford in early May 1782 to Pembroke College [29]. He was profoundly influenced by the Master of Pembroke, William Adams, who was a radical thinker and much interested in chemistry. It is here that Smithson probably first developed his infatuation with American ideology and the concept of Jeffersonian democracy. Smithson traveled extensively and wrote about minerals and crystals. He published 27 papers on chemistry and mineralogy. He was highly regarded by the small, elite society that he was privy. Smithson's last published paper with the Royal Society was "*A Few Facts relative to the Colouring Matters of Some Vegetables*" published in 1817 [34]. He was interested in the red coloring or organic materials that might be indicators of acid/base interactions. His health had become increasingly a problem, but from 1814 to 1825 he managed to publish 17 of his total scientific publications and he returned to Paris.

Smithson was eagerly investigating and collecting during his final illness. After writing his last will and testament, some 200 non-published manuscripts were sent to the United States and the Smithsonian Institute, but the fire of 1865 destroyed much of James Smithson's notes and observations. His last paper was not on minerals but on refuting the claims of the theory of the universal deluge (Noah's Flood) supported by recent work of William Buckland on his findings at the Kirkdale Cave. He is at his writing best in this treatise entitled "*Some observations on Mr. Penn's Theory Concerning the Formation of the Kirkdale Cave*" [35]. "*It is in his knowledge that man has found his greatness and his happiness, the high superiority which he holds over the other animals who inhabit the earth with him.*" Smithson returned to London in the spring of 1825 to prepare for his death. He had his will drawn with the following codicil, "*I then bequeath the whole of my property, subject to the Annuity of One hundred pounds to John Fitall, & for the security & payment of which I mean Stock to remain in this Country, to the United States of America, to found at Washington, under the name of the Smithsonian Institution, an Establishment for the increase & diffusion of knowledge among men*" [29]. Richard Rush, son of the Revolutionary physician, Benjamin Rush, was sent to England to make the necessary transfers. John Quincy Adams became the leading proponent to make an institution and museum, but Congress took until August 10, 1846, to approve of the plan. In December of 1846, Joseph Henry was appointed by the regents to be the first secretary of the Smithsonian. Charles Doolittle Walcott, his fourth and perhaps most famous successor and known kidney stone sufferer, took the reins from 1907 to 1927. Kidney stones at the Smithsonian are not currently referenced in their rather significant stone and mineral collection but the National Museum of Medicine (formerly the Army Museum has an extensive collection as does the William P. Didusch Center for Urologic History). Three years following Smithson's death, in 1832, Francois Beudant named a new mineral originally described by Smithson, zinc carbonate in his honor, smithsonite [29].

William Whewell (1794–1866) has become iconically linked with science and the term scientist. This really is limiting to both his life and his legacy [36]. In his lifetime, Whewell was a towering intellect and widely recognized for his contributions to science. Whewell was born on May 24, 1794, in Lancaster. He was quite athletic and pugilistically inclined though gregarious; he made friends easily and these often lasted lifetimes. He received a fellowship at Trinity College of Cambridge in 1811. Trinity had a powerful tradition of scholarship including the giants Francis Bacon, Isaac Newton, and Lord Byron. We've already mentioned his role in the "Philosophical Breakfast Club" that included his friends from Cambridge: Charles Babbage (inventor of the first mechanical computer amongst other innovative devices), Sir John Herschel (son of Frederick William Herschel who discovered Uranus) who became a famous astronomer in his own right and became a major influence upon Charles Darwin, and much less-known Richard Jones (clergyman and economist) [6]. Whewell was strongly influenced by one of his professors, E.D. Clarke, who was a popular lecturer of mineralogy. Also Francis Wollaston was the Jacksonian Professor of Natural Philosophy (older brother of his friend William Wollaston). Whewell won the Chancellor's medal for poetry in 1814. Sitting for this Tripos examinations, Whewell took a second wrangler and he joined the Cambridge Union Society. William Whewell practiced science and was a historian and philosopher of science for over 51 years as well as becoming the Master of Trinity College on November 16, 1841. But his primary title for much of his career was professor of mineralogy at Cambridge [37].

Whewellite is the mineral named after William Whewell and is commonly referred to as calcium oxalate monohydrate (CaC_2O_4 *H_2O). Henry James Brooks (1771–1857) first described this mineral in 1840, and another mineral is named in his honor, brookite. Whewellite is uncommon or rare in natural minerals but more common in biologic processes. These are the dumbbell crystals which are small, smooth, botryoidal to globular, and yellow-green (olive green) to brown in color [38]. Papillary concretions tend to predominate with whewellite, but they often have an apatite nucleus. Jackstones of the bladder also tends to be composed of whewellite. This crystalline form represents a difficult type of calcium oxalate stones to fragment with extracorporeal shock waves.

Weddellite is named after James Weddell (1787–184) who was the great Antarctic explorer and discoverer of the sea that bears his name. He also has a species of seals named after him, *Leptonychotes weddellii*. This mineral was found in sediments from the bottom of Weddell Sea by naturalists in 1942. Weddellite is calcium oxalate dehydrate (CaC_2O_4 *$2H_2O$). These are the Maltese crossed crystals (tetragonal dipyramidal) that commonly make up the calcium oxalate stones. These yellowish crystals tend to form sharp spicules on stones. It should come as no surprise that weddellite can dehydrate to form whewellite and are commonly found together in calcium oxalate stones. More commonly however weddellite follows whewellite in depositional sequence. They tend to make up stones that break up or comminute easily by extracorporeal shock wave lithotripsy [39].

Apatite is one of the oldest named minerals, derived from the Greek "I am misleading," referring to the many instances it is confused with other minerals such as beryl, quartz, nepheline, and calcite. It can form with either the hydroxyl group or the carbonate group substituting for a phosphate. The hydroxyl form is most commonly associated with calcium oxalate stones, whereas the carbonate form is more common in struvite stones [40]. Apatite is essential for the body because it is found in bones and teeth. It is often just called calcium phosphate but chemically it is $Ca_5\ (PO_4)_3OH$. Apatite can form the nucleus of stones and is soft, often a white powdery consistency though it can be transparent. A second form of apatite is massive, glassy, yellow-brown, or even blackish. This substance commonly accompanies other types of mineral substances of stones, and Prien and Frondel have hypothesized that waves of saturation alternate the glassy and powdery laminae in stones [41].

Struvite is named in honor or despairingly after Heinrich Christian Gottfried von Struve (1772–1851). He was a Prussian naturalist from a large family of scientists. Struvite was first discovered in bat guano or feces in 1845 by Georg Ludwig Ulex of Sweden and has a classic coffin-lid appearance (orthorhombic pyramidal). This mineral was initially and erroneously referred to as "triple phosphate" and was also referred to as guanite [42]. It is in human urine, a complex crystalline substance that occurs secondary to urea-splitting bacterial infections, particularly from the organism *Proteus mirabilis*. These infections too are linked to periodic precipitation patterns that we will discuss later [43]. Its chemical formula is $MgNH_4PO_4$ *$6H_2O$.

Brushite is the mineral named after George Jarvis Brush (1831–1912) who was a mineralogist from Yale University. He was a ravenous collector of minerals for the museum and at his death he left over 15,000 specimens to the Peabody Museum. The mineral was named in 1864 by G.E. Moore [42]. The chemical composition is $CaHPO_4$ *$2H_2O$. Monetite is a triclinic variation of brushite that is rarely identified in human kidney stones but has been seen in carnivorous animals [44].

Whitlockite is the mineral named after Herbert Percy Whitlock (1868–1948), another American mineralogist. Whitlock was a curator for the American Museum of Natural History. This mineral is most commonly found in prostatic calculi and rarely associated with kidney stones because zinc helps to stabilize this molecular structure. This mineral has been described as resinous with a brownish color [42]. Occasionally, small amounts of whitlockite has been deposited on struvite calculi and rarely in thick layers [45]. The chemical formula is $Ca_3(PO_4)_2$.

Newberyite was named after an Australian chemist James Cosmo Newbery (1843–1895). Newbery also served as curator for the Melbourne Museum. This mineral is very close structurally and usually found in association with struvite in guano deposits [46]. The chemical structure is $MgHPO_4$ *$3H_2O$.

One further rare mineral composition of stones is hannayite. This is named for James Ballantyne Hannay (1855–1931) who was a Scottish chemist at the University of Manchester.

It was originally discovered in the Skipton Lava caves in Australia. This has been found in association with struvite, newberyite, apatite, and the calcium oxalates. This has been described in only five stones [47]. The chemical composition is $2Mg_3(NH_4)_2(PO_4)_4 *8H_2O$. Other minerals may or may not be scarcely present in stones either, because they are arbitrarily added or contaminates include aragonite ($CaCO_3$), calcite ($CaCO_3$), gypsum ($CaSO_4 *2H_2O$), halite (NaCl), and vaterite ($CaCO_3$) [48].

Every Picture Tells a Story

Photography is the ability to record an image using chemical properties. The name was coined by one of the "Philosophical Breakfast Club" members, John Herschel, in 1839. Herschel had done the critical experiments necessary for the advancement of the chemistry of photography, but he stayed out of the fray of arguing who conceived and published first [6]. Herschel developed and published about the chemical reactions with silver solutions and the ability to stop or fix the reaction in 1819 using hyposulphites. He followed this paper with a presentation of using light to develop simple images using platinum salts in 1831. In 1826 the French investigator Joseph Nicéphore Niépce produced an image on polished pewter plates [49]. On January 7, 1839, Niépce's partner was Louis Daguerre who refined the silver nitrate process to produce higher-quality images with the silver deposited upon copper plates announced his daguerreotype. Since May of 1834, a fellow chemist and friend of Herschel's was also working on silver salt-impregnated paper that could be fixed using Herschel's hyposulphites, called a calotype. He demonstrated his technique on January 25, 1839, with Michael Faraday at the Royal Institute.

John Herschel graduated from Cambridge after taking top honors in his Tripos examination in 1813. He was named the youngest fellow ever of the Royal Society that same year. Though pursuing the law, he began investigations in chemistry and reported to his friend Babbage a new acid which he called "*hyposulfurous acid*" (sodium thiosulfate). He could now dissolve silver salts; this would come to his advantage when he became interested in photography [6]. He also began to investigate the optical properties of chrystals, reporting "*This salt has the most remarkable optical structure of any chrystal I have yet examined, and presents phenomena of quite a unique kind*" [6]. This property was pyroelectricity. Herschel eventually joined his aging father in astronomy in the summer of 1,816, but he continued his chemical investigations and the development of photography for studying the universe.

Photography has had a substantial impact on the diagnosis and management of urolithiasis. As early as 1893, Albert Musehold described an apparatus to photograph the endoscopic appearance of the pharynx [50]. Nitze who was pioneer in developing the first clinically usable scope to visualize the bladder (cystoscope) published the first photographic atlas of the pathology of the urinary bladder in 1893 which included the first photograph of a bladder stone in situ (Fig. 17.2) [51]. On December 30, 1926, Clarence Weston Hansell, an RCA engineer, wanted to view images from a distance using fiber optic bundles [52]. Henning and Keihack published the first color photographic pictures of the stomach in 1938 [53]. Rudolf Schindler developed a rigid and then a semirigid gastroscope, and Heinrich Lamm tried to reproduce Hansell's findings with fiber optics as a third-year medical student using commercially available materials. These findings pale in significance to the use of photography to document the location and presence of stones in the urinary tract using X-rays. The first X-ray to demonstrate a human kidney stone was Professor John Macintyre's film after first experimenting upon stones in vitro. Macintyre presented the case of a patient previously explored at the Glasgow Royal Infirmary in *The Lancet* on July 11, 1896 [54].

Liesegang

Raphael Eduard Liesegang (1869–1947) was a colloid chemist. He was the scientist who discovered the periodic precipitation reactions in gels that bear his name, Liesegang rings. Raphael was

Fig. 17.2 Nietze's work and the first published photographs of bladder stones

devoted to science throughout his life. His first book was called *Die Organologie* published in 1892 [55]. In this treatise we gain a glimpse in his ideas of chemistry: "*The trend toward a unified physical appreciation of nature can already be found over two thousand years ago as the basis of natural science of the ionic philosophers. It culminates in an attempt to find a law which is valid for all branches of science and can alone explain all facts. First I shall attempt to find this axiom for the organology. In the next volume I shall attempt the same for inorganology, and finally I shall attempt to eliminate the dualism between organic and inorganic*" [56]. Like the alchemists of old, he had crossed over to a belief in experiment and observation, the ability to measure and distill. In effect what he was proposing was nothing short of the bridge between life represented by organic molecules and the nonlife via inorganic molecules. He was dedicating his life and his work to break down the barrier between organic and inorganic chemistry using his colloidal investigations. He studied colloidal silver solutions and their use in photography. Liesegang thought that compared to the electron released from the Br^- ion by a light quantum from the masculine sperm, Ag^+ behaved like the feminine egg. The photographic process was likened to embryonic development [56].

Liesegang patterning is a special type of chemical pattern formation in which spatial order follows density fluctuations in weakly soluble salt solutions. Liesegang was a chemist interested in photography and experimental gelatin layers impregnated with potassium dichromate in 1896 (Fig. 17.3). When a drop of silver nitrate was added, a precipitate formed concentric bands radiating outwards. The distances between each ring always increased with the distance from the center. Liesegang systematically pursued this phenomenon of spatiotemporal precipitate patterns, which he referred to as "*quasiperiodic precipitation*." Wilhelm Ostwald popularized Liesegang's findings in his book of general chemistry in 1897, calling the phenomenon an extension of supersaturation theory. It was Jablczinsky who described the mathematics of the periodic banding as a geometric series in 1923. Now sophisticated computer modeling schemes generate many of the aspects of Liesegang rings [57].

Liesegang Rings

Periodic precipitation patterns had attracted interest at least since 1855 by Friedlieb Ferdinand Runge (1794–1867) who noted periodic banding on filter paper which he called "*self-painting pictures*." Runge is today a relatively unknown physician whose works are lost in the labyrinth of specialized scientific history. He was born on February 8, 1794, in Billwerder, a small town

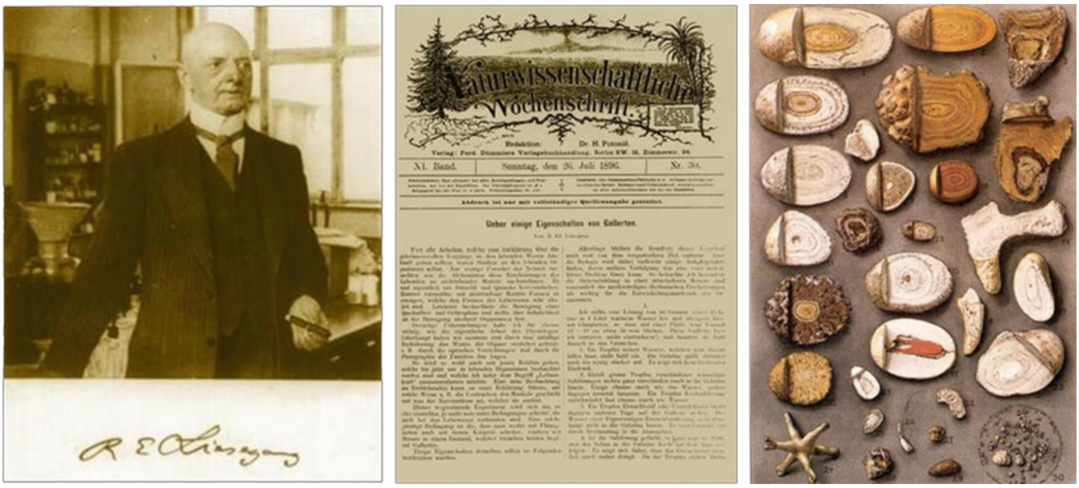

Fig. 17.3 (**a**) Liesegang, (**b**) his famous paper on periodic precipitation, and (**c**) Liesegang rings in stone disease as famously depicted in Howard A. Kelly and Curtis F. Burnam's *Diseases of the Kidneys, Ureters and Bladder* by Max Brödel [82]

near Hamburg. He was apprenticed to his uncle, a pharmacist, at the age of 16 but went on to medical school at the new University of Berlin but graduated from Jena in 1819, writing a thesis on his investigations of atropine, derived from the plant belladonna [58]. He published a two-volume book on biologically active plant chemicals in 1820 and 1821 and obtained a Ph.D. in chemistry from Berlin in 1822. He wrote many books and papers on chemistry through the years, but he became interested in the chemistry of colors while a professor at Breslau in 1826. In 1834, 1842, and 1850 he published a three-volume work on *The Chemistry of Coloring* (*Farbenchemie*) [58]. It is in this third volume on the preparation of dyes when he noted using filter paper for testing dyes, "*due to its capillary force it separates a drop spotted on it into its components and…creates a picture with a dark colored center part and lightly colored or even colorless rings on areas*." Runge was interested in his colored filter paper's patterns and privately printed his *Musterbilder* which in English is "*To Color Chemistry*. *Pattern Pictures for the Friends of Beauty and for Use by Draftsmen*, *Painters*, *Decorators and Textile Printers*, *Prepared by Chemical Reactions*" and was dedicated to King Frederick William IV. Though these chromatographs represented the first use of paper chromatography (honor was given to M.S. Tswett in 1903), he was becoming more artistic and philosophical regarding his images. He published 5 years later an expanded new book of his filter paper images called "*The Driving Force of Formation of Substances Visualized by Self-Grown Pictures*" (often called *Bildungstrieb*) [58]. Each color illustration of both books were individually created by Runge and glued into the books (though he used children to actually place the chemicals on all of the filter papers for the books). Runge received a special medal for this work at the 1855 World Exhibition in Paris and later at the 1862 World Industrial Exhibition of London [58].

It is fascinating that Runge came to believe that his patterns were created secondary to a mysterious "driving force" that he incorporated from his former professor, J.F. Blumenbach (1752–1849), at Göttingen. This is also similar to Liebig's "vital force" in organic chemistry and perhaps Mesmer's animal magnetism that was debunked by a scientific investigation that involved Benjamin Franklin in 1784. But another clear influence upon Runge came from Johann Wolfgang von Goethe (1749–1869) who he met while a student in Jena between 1818 and 1819. Goethe published his own Farbenlehre (The Science of Colors) in 1810 where he sought a transcendent meaning to coloring as well [59]. This was also picked up by Karl von Reichenbach (1788–1869), another chemist who introduced the idea of "*the Od*," a hypothetical force that pervades all of nature [60]. Since we are discussing patterns, it is fitting to curcle back to the final self-published edition of Runge's, a single copy of his *Bildungstrieb* where he inserts "*The Od as the driving force of formation…*" [61].

Tree rings have fascinated investigators for centuries and the links of these rings to dating go back for many years. The actual science of tree ring dating has been attributed to the growth of science following World War II [62]. The growth of these tree rings provides impressive abilities to date archeometrically, and newer strategies allow investigation of fossilized trees as well extending the dating strategies to over 12,460-year-old oaks [63]. Saturn's rings represent another periodic precipitation pattern that consists of ice and dust particles that encircle the sixth planet from our sun. The rings were first sited by Galileo in 1610 but he was uncertain as to what they were. They were identified by Christian Huygens in 1655 and again later by Hooke. But it was Giovanni Cassini that determined that there were multiple rings and began to note a pattern to them in 1675 [64]. Each planet in our solar system is also arrayed in a rather regular precipitant pattern, and each have a right-handed spin. Biologically, corals grow with annual ring formation patterns that also seem to be from periodic precipitation [65]. Not surprisingly sedimentary rocks themselves were first studied by Nicolas Steno for their periodic banding stratification. Finally, in pathologic processes that result in sporadic inflammations such as xanthogranulomatous pyelonephritis, inflammatory breast disease and other sites that laminated structures can result [66].

So Liesegang rings are simply a naturally occurring series of either circular (one dimension) or banded geometric, nonuniform spatial distributions of materials. Though attributed to Liesegang, others certainly noted these occurring and have commented upon them over the years. Research into Liesegang phenomenon is extraordinary and now involves complex computerized modeling and mathematical probability equations. Ostwald was a chemist who first proposed that supersaturation represented the driving force to the creation of Liesegang ring formation and distribution. Nowadays, complex laboratory methods can keep supersaturated urine solutions constantly mixing to measure and investigate the kinetics of crystal precipitation and aggregation [67]. Growth models can be formulated [68].

Supersaturation Theory

As urine becomes supersaturated with mineral components, usually cations and anions which are filtered by the kidneys, then the risk for precipitation increases. The physics of this process is now well known, and the physical chemistry that drives this process is also well described.

George Rainey (1801–1884) is principally known as an anatomist and was born at Spilsby, Lincolnshire, in 1801. He was apprenticed to a doctor and self-educated in Latin, Greek, and mathematics. He served as assistant to Mr. Barker, a local surgeon in Spilsby, prior to becoming a student at St. Thomas's Hospital in 1824. Not wealthy, he supported himself by tutoring others and developed keen skills as a teacher. He especially was good at anatomy and for the next 10 years was a private teacher at the medical school until he developed tuberculosis. He went to Italy in 1827 to recover and returned to become the curator of the museum and demonstrator of anatomy at St. Thomas's Hospital. George Rainey was another surgeon and anatomist who developed an interest in chemistry and influenced many others including Henry Vandyke Carter, William Ord (who we will meet later), and Lionel Beale [69]. Rainey early experimented upon plant life. "*An Experimental Enquiry into the Cause of the Ascent and Descent of the Sap, with observations on Endosmose and Exosmose*" was published in 1847 [69]. He became interested in microscopic pathology publishing in *Proceedings of the Royal Society* in 1846, the *Philosophical Transactions* in 1850 and 1857, and the *Medico-Chirurgical Transactions*. He became very interested in the organic/inorganic processes

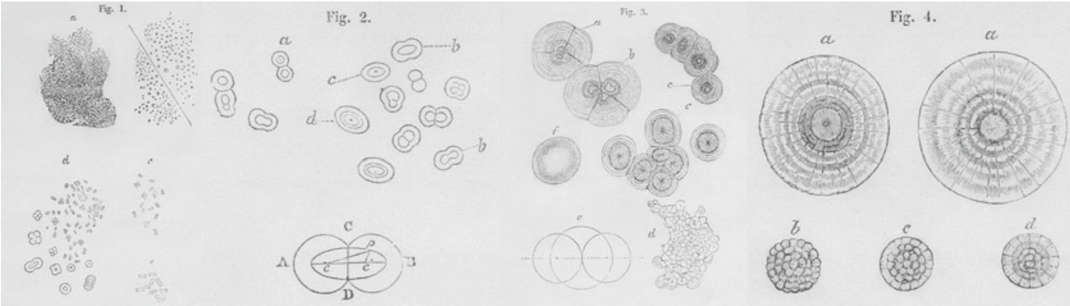

Fig. 17.4 The first four illustrations of George Rainey's model of actual stone formation

of animal shell production and the formation of bones. In 1858 Rainey produced a substantial work on the formation of animal shells and bone. The treatise was entitled "*On the mode of formation of shells of animals, of bone, and several other structures, by a process of molecular coalescence, demonstrable in certain artificially formed products*" [70]. Even negative reviews of his theories praised Rainey's minute observations.

He began his book by pointing out methods for those who question his findings to pursue themselves, and he opens up his collection of specimens to those who wished to observe for themselves. This was quite in keeping with the motto of the Royal Society, "*Nullius in Verba*" or don't take anyone's word for it [71]. He began with his observations on the formation of shells of animals. He would use his methods of microscopic examination, chemical identification, and experimental artificial models to formulate his theory of coalescence. This is prior to the actual biochemistry and intracellular physiology, but his methods were truly amazing. His first four figures show how in an ex vivo supersaturated solution stones actually form (Fig. 17.4) [70]. He called the formation of globules of crystalline substance, in this instance carbonate of lime coalescence, and believes that it naturally forms into spheroidal patterns by mutual attraction and gravity. It was the method of concentric lamination from which he made his bold observations. On page 18 of this work he states, "*Hence, prior to the complete coalescence of any number of spherical particles into one sphere, each particle or spherule must undergo a process of disintegration (or be taken to pieces), an after that, the molecules of the disintegrated spherules must be put back together again under the same static conditions as they were before*" [70]. He continues by stating "*Hence the careful inspection of specimens exhibiting these different stages of coalescence brings to view numerous examples of calculi with concentric lamiae (as shown in Figs. 17.2 and 17.3)*" [70]. So now we can proceed to his model of stone formation: "*The first stage in the formation of such calculi is a spherical conglomeration of those globules producing a mulberry-like appearance, (See Fig. 17.4b–d) and form closely resembling that of the corpuscle called by pathologists a glomerulus, although that is composed of particles of oil. The next is the disintegration of these spherical particles which takes place first in the peripheral ones. In this process every vestige of their original form and structure is destroyed, and they become reduced to amorphous granular mass. Next, the molecules nearest the surface coalescing, form a clear ring completely surrounding the amorphous matter occupying the interior. (See Fig. 17.4b) The further progress of the process of disintegration and subsequent coalescence is marked by the increase in width of the circumferential bright ring, just as the central amorphous part diminishes, showing that the one is formed at the expense of the other, (See Fig. 17.4d) until all the latter has disappeared, and is replaced by a succession of bright concentric laminae*" [70].

Modern Science and Phases of Precipitation

We have discussed throughout this chapter on crystals, stone formation with crystal aggregation, stone growth, and the role of periodic precipitation patterns common to all stone formation. But stone formation occurs in the urine of humans and it is time to look at the urine itself [72]. Since prehistoric times man was first able to only look at the color of the urine and perhaps any gross materials that might occur. The ancient Babylonians and Egyptians added taste, color, odor, and sedimentation to the urinary evaluation. Hippocrates in his aphorisms stated, "*When the urine of a man with fever is thick, full of clots and of small quantity, an increase in quantity and clarity is advantageous. Such a change is especially likely to occur if, from the beginning or very shortly afterward, the urine has a sediment*" [73]. The Middle Ages added the macula to the science of urinary evaluation but also led to the rise of the "Pisse Prophets" [74]. The French microscopist Fabricius Nicolaus De Peiresc (1580–1637) first turned a high-powered look into urine sediments in 1630. He is reported to have stated that the urine looked like "*a heap of rhomboical bricks*" [75]. Robert Hooke again looked at urine as well and drew some of the first urinary crystals in his 1665 *Micrographia*. Hermann Boerhaave carried out studies of urine to investigate if crystals in the urine were normal, common, or caused by certain types of food and drink in early eighteenth century. James Tyson (1841–1919) published one of the first practical guides to urinary examination in 1870 [76].

Crystalluria is a condition in which urinary crystals occur in human urine. In most cases, this condition is transient and apparently completely normal. Crystals can be those that make of pathologic stones such as calcium oxalate, uric acid, and amorphous phosphates. Struvite and cystine crystals are almost always pathologic. Since crystals are the building blocks of stone disease, it is little wonder that they have been studied extensively as a condition that progresses to disease. In 1969, Robertson and colleagues reported that stone formers though having about the same quantity of crystals in their respective urines had larger crystals (10–12 μm vs. 3–4 μm), and they noted crystal aggregation or clumps [77]. Numerous other authors have sought to redefine these risks using sophisticated methods but there still appears to be great controversy. The amount and size of crystals has likewise been utilized to monitor therapeutic effects of medications such as orthophosphates, thiazides, citrate, and pyridoxine. So, there are many variables that affect the supersaturation of urine including the presence or absence of other illnesses (such as gout or leukemias), the state of hydration, the ambient temperature and humidity, the diet, bone health, and bowel function. Even this simplifies things a bit but more on this later. A recent music video from Western University highlights the chemistry, the suffering, and the social interactions associated with stone disease [78] (http://www.mineralogynetwork.com/brainbios/video/145246).

Conclusions

> "*What is man, the son of man, asks the biochemist, but a container of salt solution in a state of more or less saturation? Ever so slowly he settles out, clouding milkily up, depositing within himself silt, a silt whipped by the slowest of currents and inner winds into serrated banks and whorls. Who knows at what point the balance between solution and precipitation will have been tipped, and the first speck of mineral will appear like the \birth of a planet in the void, realizing out of tissues overcharged calcium, uric acid or others of the stone-forming elements, a mote, a jot, unbeknownst, uncelebrated? No tocsin is sounded, no alarum. Yet toxin and alarm are its business credentials. When is it that the acidity or alkalinity of the urine is so mysteriously altered, and with such a misdirected hospitality, as to encourage the persistence of the wicked speck? Too small by many months, even years, to be seen or felt, it is most importantly THERE, either lodged in some damp cul-de-sac, or carried by hidden currents, crashing against secret membranes, all the while gathering unto itself from the high urinary waters, full as briny as the Dead Sea, more and more of the bitterest crystals, grow slow as a diamond, and as cursed, worn only at the greatest peril*" [79].
>
> —Seltzer, Richard: Mortal Lessons. 1974.

Minerals are naturally occurring substances that form solids at room temperatures and are distinct from rocks that can be aggregates of minerals. Human urolithiasis can therefore be both minerals and rocks. But the substantial building blocks of all urolithiasis are the minerals. These make up as much as 90 % of most stones, although there are those rare human stones that are mostly proteins. Hematin is one such stone that forms very rarely; also indigo stones and other chemically or drug-induced stones fall into this category [80]. Mineralogy is one of those ancient sciences that literally exploded from the sixteenth to the seventeenth centuries and gave rise to the studies of crystals themselves. Crystal science is intimately tied up with physics and mathematics because of the geometry of crystal lattices and the peculiar effects that crystals have upon light and color. The early scientists in these fields also crossed over to the study of light itself and the development of modern photography. All of these peculiar sciences are quietly linked to urolithiasis but as shown in the preceding sections, at times loosely. This brings us to the very basics of science itself that ties this story of sorts together, the "Philosophical Breakfast Club" of Trinity College [6].

During the times essentially covered during the bulk of this chapter, the scientific community was undergoing significant upheaval. The British Association for the Advancement of Science (also shortened to the BA) was proposed and held its first meeting on Tuesday, September 27, 1831, in York. The prime movers were all somewhat disenfranchised with the Royal Society and were seeking alternative venues to advance the cause of scientific investigation. On June 24, 1833, the British Association for the Advancement of Science met for the third time. William Whewell who was one of the guiding lights in the formation of this organization rose in response to Samuel Taylor Coleridge's remarks that members should no longer be called "*natural philosophers*" which created an uproar. Whewell rose and suggested that if "philosophers" was too lofty a term, "*by analogy with artist*, *we may form* '*scientist*'" [6]. Curiously the BA also recommended against the most significant instrument created by one of the "Breakfast Club," Charles Babbage's analytical engine which would have been the world's first computer in 1878. Also the venue for the BA also launched the famous debate created by Darwin's Origin of Species when Thomas Henry Huxley and Bishop Samuel Wilberforce clashed at Oxford in 1860 at the thirteenth annual meeting.

Liesegang initially described the process of the periodic precipitation reactions in gels; others would continue to describe this same process in other biologic and natural systems, such that the literature on this subject is absolutely massive. Examples include the pigmentation in animal's irises, the Haversian canalicular system of bones follow this pattern, as does Rainey's beloved clam and oyster shells amongst a wide array of naturally occurring structures.

The Crystal Palace was an iron and plate glass building constructed in Hyde Park, London, for the Great Exposition of 1851. There were more than 14,000 exhibitions including the "*crystal fountain*" which was a light-guided illumination taking advantage of total internal reflection of light that would later be able to illuminate fiber optic endoscopes in the modern treatment of urolithiasis and lasers that would evolve into the devices used to destroy stones [81]. In addition, Persian cats were shown for the first time at the Crystal Palace, and they notoriously develop calcium oxalate bladder stones. Dinosaurs were demonstrated for the first time with gigantic renditions created by Benjamin Waterhouse Hawkins and the physician/anatomist and sometimes nemesis of Charles Darwin but great friend of Wollaston, Richard Owen. The Crystal Palace came to represent progress as did crystallographers in the science of mineralogy.

Niels Stensen (aka Nicolas Steno) investigated crystals, mineralization, and the ideas of stratification of sedimentary rocks as well as being a gifted anatomist. In addition, he had a crisis of faith, having been born and raised in the Protestant stronghold of Denmark. After so much academic effort, this truly gifted individual gave it all up to become a Roman Catholic priest. His rise was also quick in this new profession and he became the Bishop of Titiopolis or the north in order to attempt to return Catholicism to Germany. He resigned as bishop in 1685 when he became ill. Some say he suffered from stone disease, some from gallstones, and others from colon cancer. He died on December 6, 1686, living and writing in poverty and suffering colic as only stone patients can imagine. He was initially buried inconspicuously but was moved at the request of the Medicis to their tomb in San Lorenzo. The grave was again opened in 1953 to a new chapel called Capella Stenoniana with a Latin epitaph:

Here rest the remains of Niels Stensen, Bishop of Titiopolis, a God-fearing man.
Denmark gave him a life of heresy, Tuscany gave him a rebirth in a true faith.
Rome in bravery honored him by a bishop degree.
Germany had a heroic announcer of the gospel.
Schwerin lost him completely crushed and suffering for Christ.
The Church has mourned him. Florence wanted to won at least his ashes.
Anno Domini 1687.

Steno was consecrated by the Vatican in 1938 the occasion of his 300th birthday. On October 23, 1988, Pope Pius Jan Pavol the Second proclaimed this quiet physician/anatomist and scientist a saint.

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18 Lithotomy

Introduction

> "*The blacker the past, the brighter the hope for the future*." [1]—Francis Bacon
> *Thoughts and Conclusions*

Stone disease represents one of those "*concrete*" medical maladies where there was never any good medical alternative to surgery until the modern era. In fact, the evolution of surgery itself has been linked to "*cutting for the stone*" since the earliest descriptions. By stone disease we are of course referring to bladder, prostate or urethral stone disease. These were amendable to treatment by the earliest surgeons. The term surgeon itself is probably not an accurate reflection of the earliest itinerant stone cutters. They were most likely tradesman, or familial descendents of stone cutters.

Since mankind evolved into a self-aware creature, the ability to impart some type of control over health and disease probably also co-evolved. Since disease is universal, there also probably has been some attempt by man to intervene and not simply die peacefully in the night. There is anthropological evidence that medicine first evolved from man's earliest attempts to find spirituality in his grasp for his/her place in the cosmos. The first medical practitioners were closely aligned with religious beliefs, or shamans. Acts of mercy were quite probably equal in performance as were acts of wickedness, and since no human being is quite unique from the rest of the lot of humanity, so too medicine cannot be fully removed from historical consideration when it comes to depravity. It is almost prophetic that the symbol of medicine is the serpent; entwined in some symbols upon the staff of Asclepius [2]. The serpent represents a sinister presence in the foundations of Western religions. It is the serpent that convinces Eve to consume the apple of knowledge. The caduceus is another ancient symbol that has become linked with medicine and its principles. It is most often depicted as a winged-staff, first associated with the god, Hermes. There are one snake caduceuses and double snake staves. The original rod of Asclepius had only a single snake and no wings. William Hayes Ward believes that the first iconic representation for medicine occurred between 3,000 and 4,000 BC, or almost 5,000 years ago [3]. Despite the wealth of historical information and scholarship regarding modern medicine's iconography, the serpent and the snake are now a fixture. The serpent with its potential as both the harbinger of evil or source of hope in overcoming the evils of nature that afflict mankind clearly evoke both sides of modern medicine. Again, the historical symbol depicted in the famous sculpture of Laocoön, showing the wrath of Apollo upon the family of the Trojan priest who tried unsuccessfully to prevent the acceptance of the veiled gift of the Greeks, the great wooden horse. As punishment for attempting to defy the gods, Laocoön and his two sons become attacked by two mighty serpents [4]. Though medicine has evolved into a young science with our burgeoning abilities to intervene and save lives; suffering

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persists, inequality lingers, man's inhumanity to his fellow man endures, and medicine's darker sides must not be forgotten.

At the dawn of mankind's understanding of human disease, a group of investigative and inquisitive physicians created a cult-like school on the distant isle of Cos in ancient Greece. They practiced, wrote, taught humane care of the sick, and postulated the morals that might make medicine great. Yet it is absolutely striking, that this gifted and highly cerebral lot never incorporated virtue (arête), moral excellence, wisdom, and courage to fight for the cause of the patient into the ancient prescription for health care. The Oath of Hippocrates is the classic piece of ancient medical literature that is most often associated with early medicine, but like the words themselves much of its origins, meanings, are simply unknown [5]. First, Hippocrates had never commented upon the Oath, nor recognized it or its suppositions. The first written version that is known was written in 300 CE (current era), making it about 700 years off from the time of its supposed composition. The Oath consists of about 400 words that has lost some of its meaning as it swears to an Olympian god, disavows surgery, promotes paternalism, and is altogether a bit ritualistic in our more enlightened sense [6]. But it is a vital historical document in the history of medicine and provides us with some early insight into the heritage and legacy of medicine. By swearing to the god, Apollo who was the son of Zeus and naming his son, Asclepius and two granddaughters Hygeia and Panacea the myth of medicine has its origins [7]. Asclepius was the illegitimate son of Apollo and Coronis (human who lived in Larissa, Thessaly which is not far from the island of Cos). Asclepius was born when Apollo arranges to have Coronis murdered for infidelity. Asclepius was trained as a physician by the centaur, Chiron and married another human woman, Epione. They had five divine children (four daughters and one son) and two human sons. The divine children were Hygeia (daughter and goddess of health), Panacea (daughter and goddess of remedies), Iaso (daughter and goddess of medicine), Aigle (daughter and goddess of radiance), and Telesphorus (son and god of convalescence). The two mortal sons are Machaon (physician and healer that dies in the Trojan horse incursion into Troy) and Podalirius who survived the Trojan War (c.1200 BCE) and moved to the Ionian coast to practice and whose descendants developed the school on Cos (legends link this family to Hippocrates) [8].

But the Oath is a standard symbol of the role of physicians in society, it is a codicil of rules to obey, and sets the mark for evolution of medical ethics. Modern medicine, like ancient medicine represents a paradox as it did then. Ancient Greek medicine cured very little disease (estimates were that 2/3 of sick patients died under a physician's care). They really were the first to separate the treatment of disease as a natural process, not linked to the belief in divine intervention. Today we offer ever increasingly sophisticated technology, but the patients perceive a decline in trust of healthcare. We have eradicated smallpox, polio is almost extinct, and even some types of cancer can be completely cured. Yet patients decry the need for a sympathetic physician, one who takes the time to know and care about them. Compassion has taken a back seat to technology. Oaths do serve a purpose and several surveys of American Medical Centers have been reported. From 1959 oath-taking at medical school graduation ceremonies has increased from 79 % to almost 100 % since the 1970s [9]. A total of 158 US allopathic and osteopathic centers all use the Hippocratic Oath, the Prayer of Maimonides, the Oath of Louis Lasagna, or a modified version often with input from the medical students. Oaths embody the aspirations of the profession. They imply obligations and duties on young physicians at the outset of their careers. Modern modifications make up for the lack of humanism that personifies the patient and makes them a partner in health and disease [10]. Some oaths now include specific pieces regarding public health, social responsibility, and patient advocacy. Medicine has learned from the mistakes in the past.

Ancient Art of Lithotomy

The following historical digression into the Hippocratic Oath was simply to begin with the admonition as follows "*I will not use the knife,* *not even on suffers of the stone, but will withdraw in favor of such men as are engaged in this work*" [11]. Edelstein goes into some great historical details on the separation of the earliest health care providers as to physicians who deal with internal medicine and prescriptions and surgeons who would be asked to cut for the stone since they are below the dignity of the learned physician. He points out the medical historian Litttré does not accept this classic argument, but thought perhaps the "Oath" intended this for surgical castration [12]. But other historians suggested that the Pythagorean physician who first actually adopted the oath probably recoiled against the risk of impotence from surgical lithotomy. It is now thought that the oath was just guiding physicians to use a specialist, the first named specialist in antiquity [13]. There is no mention that a physician might get the required training to become that specialist however [14]. There is no modern way to further interpret this cryptic passage in the Hippocratic Oath. Our only truly ancient source left is Aristoxenus who said, "*they believed most of all in diatetics; they applied poultices more liberally than did their predecessors, but thought less of the efficacy of drugs; they believed least of all in using the knife and in cauterizing*" [15].

Before we embark on this sojourn through the earliest histories of surgical lithotomy, it is imperative to review where the primary sources come from. Let's turn momentarily to Sir. William Osler yet again and ponder his *The Beginnigs of Modern Medicine* which debuted in 1913 as the Silliman Lectures at Yale University [16]. Quoting him liberally is always a good idea:

> "*To one small people…it was given to create the principle of progress. That people was the Greek. Except the blind forces of Nature nothing moves this world which is not Greek in its origin.*" [16]

He continues:

> *After flowing for nearly 1,000 years in the broad plain of Greek civilization, the stream of medicine is apparently lost in the morass of the middle ages; but though choked and blocked like the White Nile by the Sudd, three channels may be followed through the weeds of theological and philosophical speculations. One may be traced in the direction of the Eastern Empire where great Byzantine compilers, Oribasius, Aëtius, Alexander of Tralles, Paul of Aegina carried away in the their writing much that was of value in Greek medicine. With the fall of Constantinople in 1453, and the dispersion of many Greeks, there came to Italy scores of learned men with literary treasures—rich pablum for the Renaissance.* [16]
>
> *A second stream may be traced, though with difficulty, through Southern Italy, always a stronghold of Greek thought. The origin of the famous school of Salernum, a town about 30 miles southeast of Naples, is lost in obscurity, but when it comes into prominence in the 9th and 10th centuries, we find it already the seat of a flourishing medical school, with lay professors, whose fame spread throughout Europe and the East.*
>
> *Until the 12th century Salernum appears to have had its inspiration from Greek or Graeco-Roman sources; later with Constantantinus Africansu Arabian medicine was introduced.*
>
> *The third and for our purposes the much more important stream flowed in Arabian channels. To change the metaphor, "from the hands of the unworthy successors of Galen and Hippocrates, these wonderful people took the flickering torch of Greek medicine, and if they failed to restore its ancient splendors, they at least preserved it from extinction, and they handed it back burning more brightly than before." (Withington)* [16]

So to Celsus and the beginnings.

Ancient sources of lithotomy included the works of Celsus and Paul of Aegia as well as the Indian writings of Sushruta and early Middle Eastern writings. But stone cutting most certainly was well entrenched prior to this. The Hellenistic Period from the time of Alexander to the beginning of the Roman Empire we have only tantalizing remnants of the scholarship and practices of this period. We do have Roman lithotomy instruments from ruins of Rimini, Marcianopolis, Ephesus and Cyrene. These dovetail rather well with the writings of Celsus [17]. We should define some terms and methods prior to getting too deeply into the art of stone cutting. Λίθος means "a stone" whereas τέμνω is "to cut." There were more than one method to cut for a stone, and virtually every approach had been tried prior to the modern era. Ammonius of Alexandria performed lithotomy in the Hellenistic era and reportedly crushed stones and extracted fragments. The Apparatus minor or "cutting for the gripe," or Celsus's method represents the method described in *Lithotomia Celsiana* [18]. This is a perineal lithotomy utilizing few instruments. Next is the Apparatus major or the Marian lithotomy also a perineal lithotomy. This was modified further into the lateral lithotomy by Frère Jacques in about 1697 who came to Paris to demonstrate his new method. The High Operation refers to a suprapubic cystolithotomy where credit is given to Pierre Franco in 1556 for performing this in a child. Next, a lithotomy through the rectum and via the vagina has also been described by various surgeons through time. The literature on lithotomy and it's history is vast, it would appear that both historically minded surgeons and specialists such as urologists take great pleasure in research of this type. Now the work is much easier since some translations of the remaining ancient literature is readily available [18].

Aulus Cornelius Celsus (c.25 BCE–c.50 CE) was a Roman encyclopedist (though he could have been a physician) who wrote his monumental *De Medicina* which much of our knowledge of Greek medical thought has been referenced. He lived in the times of Emperor Tiberius and only eight of his medical books have survived [19]. He literally represents the main source for much of the lost legacy of Hellenistic medicine that thrived in Alexandria. We will quote liberally from his Chapter 26 *On difficulty passing water and on stones and their cure*. He begins, "*As mention has been made of the bladder and of stone, this seem to be the fit place to describe the treatment to be adopted in cases of calculus, when it is otherwise impossible to afford relief; but it is most inadvisable to undertake this hastily, since it is very dangerous*" [18]. He goes on to make the famous pronouncement that the surgery is best performed in the spring and in patients from age 9 through 14 and only then if "*the disease is so bad that it cannot be relieved by medicaments or endured by the patient without shortly causing him to die*" [18]. Celsus now mentions the procedure to prepare the patient for surgical lithotomy. "*Therefore, when it has been decided to fall back on this last resource, the patient's body must be prepared by dieting for some days beforehand, so that he takes a moderate amount of wholesome and not glutinous food, and drinks water. Meanwhile he should also take walking exercise in order to encourage the stone to descend to the neck of the bladder. The fingers may be used to check whether this has happened, as I shall point out in the course of the description of the treatment. When we are sure this has occurred, the boy is to fast for the day before the operation, which must be performed in a warm room in the following manner*" [18]. The remainder of the description of the surgical procedure that would dominate the until the seventeenth century can be read at the conclusion of this chapter (Addendum) [18].

Of the second stream that Osler mentions we have accounts from Aëtius of Amida (Byzantine physician from probably the early sixth century CE), Alexander of Tralles (527–565), and Paul of Aegina (c.625–c.690). Aëtius of Amida wrote his *Sixteen Books on Medicine* and included a section on bladder stones and mentions surgery [20]. "*If stones cannot be expelled from the bladder by urinating, but stop up the urethra and cause anuria, we must set the patient on his back with his thighs much higher than the back- as has been said above- and move him to and fro and by all means in order to force the stone to slip out through the urethra. Then we must order him to urinate with as much strength as possible while still lying on his back and with his thighs upwards. Should he not succeed in passing water despite these means, we must use a catheter to let urine flow…If we fail to crush the stone in the bladder in spite of these treatments, we must have recourse to incision, which, as a rule, must be performed below, so that the stone may be extracted from the incision*" [18]. Alexander of Tralles was contemporary with Emperor Justinianus and he came from a family of physicians. He wrote his magnum opus, Therapeutics in 12 books [21]. He definitely preferred medical therapies over surgery. He states, "*Sufferers from calculi must be treated during attacks with medications that can relax, soothe, and moreover reduce and let the calculus come out*." Which brings us to Paul of Aegina who is known to have travelled extensively collecting bits of medical wisdom and he became one of the favorites of the rising Arabian scholars [22]. He wrote his *Outline of Medicine in seven books* were he discusses the method of catheterizing the patient with calculus anuria to relieve their pain and goes on to describe perineal lithotomy (also see Addendum) [18]. He appears to be speaking from experience and the Arabian physicians that followed his treatise would improve upon the instruments and techniques he describes.

The Third Stream

Osler intended in his Silliman lecture to discuss the great physicians including the Arabian and Persian dynasties but we can afford to be just a little more liberal and will include the ancient Hindu source Sushruta Samhita (c.1000–500 BC though there are suspicions it is even more recent, like 500 AD) [23]. "*The surgeon who is not well cognizant of the nature and position of the vulnerable parts in the eight srotas (ducts) namely the perineal raphe, spermatic cords, ducts of the testes, Yoni (vagina), the rectum, the urethra, urine carrying ducts or ureters and the urinary bladder and is not practiced in the art of surgery, brings about the death of many innocent victims*" [24]. Sushruta performed his perineal lithotomy with a vertical incision lateral to the median raphe. This makes the space to approach the bladder somewhat smaller than the more median incision of Celsus and more difficult to remove really large stones. Shusruta provided minutial details regarding his surgical instruments, at least 125 types with an additional 28 varieties of catheters, sounds, and irrigation syringes. He gave measurements of urinary dimensions, and advised on using metal instruments that could be cleaned with alkalis and caustics [25]. His description of perineal lithotomy comes from Chapter 7 of Chikitsa Sthanam (therapeutic measures, Addendum) [24].

Now we come to the great Middle Eastern physicians of Osler's third stream. Abū-Bakr Muhammad ibn Zakarīyā' ar-Rāzī known in the West as Razes (c.860-c.923) was a Persian born in Ar-Rayy but practiced in Baghdad. He was a compiler of the writings of Aëtius of Amida and Paul of Aegina [18]. 'Alī ibn al-'Abbās al-Māgūsī aka Abbas (930–994) was born near Jundi-Shâpûr and was believed to have practiced in Baghdad. He wrote about urinary catheterization but added nothing on stone disease. Abū 'L Qāsim az-Zahrāwī, Hhalaf ibn 'Abbās aka Albucasis was born in az-Zahrā (c.936–1010/1013). His *The Practice and Method* book 30 dealt with surgery and lithotomy. It is illustrated showing over 200 instruments and gives precepts derived from practical experience. He also gives instructions to midwives who dealt with stone disease in females throughout the Middle Ages and probably even prior to this time [18]. He wrote "*What ever I know, I owe solely to my assiduous reading of books of the ancients, and to my desire to understand and appropriate this science*. *To this have added the observations and experience of my whole life*" [26]. Al Zahrawi described the use of a sound to make a diagnosis of bladder stones. He described the delicate use of a forceps to extract a calculus without breaking. He also mentions the use of a lithotrite for crushing larger stones, too big to be safely delivered from the perineal lithotomy. He devised his own irrigation catheters and syringes [27].

Abū 'Alī al Husain ibn 'abd Allāh ibn-Sīnā aka Avicenna (980–1037) was born in Afshanah and died in Hamadhâm. His main work was the *Canon of Medicine* and appears his main source is Galen. He did include some notes on surgery, but not much on bladder stones [18]. Avenzoar was born and practiced in Seville (1090–1162) and published a work called *Book on the assistance by therapeutics and diet*. For our interest he did present some dietary guidance for preventing stones, not that significantly different from the Greeks [18]. Abū 'l-Walīd Muhammad ibn Ahmad ibn Muhammad ibn Rušd aka Averroes (1126–1198) completes this compilation of Middle Eastern physician-scholars. He was born in Cordoba and died in Marrakesh. He published his *General rules of medicine* and *Book of the whole medicine* which became the stuff of graduation theses by medical students in the Renaissance (Andreas Vesalius for instance) [18].

Surgeons and Lithotomists of the Dark Ages

That lithotomy did not die with the snuffing out of classical literature and medicine is self-evident. In Italy at least, families of "stone cutters" prospered. For a long series of generations the Norcia in Umbria and the Castello and Contado delle Preci all practiced lithotomy, probably unchanged from Celsus. Preci is an Umbrian town that was famous from the Roman times as a center of surgical education. Scacci described it as "*Pulchra Sabina Preces alto tenet aggere priscam chirugis patriam*," or "*lovely Sabina Preci keeps the old school of surgery in the high castle*" [28]. There are few and scanty writings about this old surgical school in medical history, but Lanfranco in 1306 described the Norcini in his *Chirurgia Magna et Parva*. The surgical school at Preci was certainly active between the fourteenth through the eighteenth centuries [29]. The Preci anatomical school also trained surgeons as empirics and animal surgeries, such as castrations and simple veterinary procedures. They also evolved a complex monastic affiliation with the Benedictines via the Abbey of San Eutizio which was located near Preci. After coming to Preci for training you could leave as an empiric surgeon or a professional surgeon with anatomic knowledge. The professional training took place at the St. Cosma and Damiano College where they were taught about surgeons tools and techniques. The empiric surgeons were called "*Cerusici*" or second class "*Vulnerari*" or half-surgeons. They were trained in lithotomy and some were even asked to come to the great universities such as Perugia, Bologna, and Padua. It is known that Pope Innocent IV (1249), King Luis I d'Angio and Amedeo VI (1382) had bladder stones removed by Preci lithotomists [30]. In other countries the lithotomists were called empirics, vagabonds, and became associated with barbers. Guy de Chauliac, a fourteenth century writer and surgical author stated that he never performed a lithotomy as the other "*periti*" did [29]. But towards the end of the Middle Ages, from the mid 1450s to 1500s three groups of healers were recognized, though a whole group of others were popular; physicians (practiced internal medicine), surgeons and apothecaries (pharmacists) with wide degrees of overlap. Elaborate rules of practice were codified during these years and we will examine the *London Rules for Surgeons* [31]. "*First, it behoves a surgeon who wishes to succeed in this craft always to put God first in all his doings, and always meekly to call with heart and mouth for his help, and sometimes give of his earnings to the poor, so that they by their prayers may gain him the grace of the Holy Ghost*" [31]. It follows a Hippocratic pattern thereafter with discussion of cleanliness, intemperance, and the like. It also talks about surgical fees, with the admonition "*If he does undertake a case, he should make a clear agreement about payment and take the money in advance*" [31].

We have previously presented the star surgeons of the Dark Ages. The Dominican friar Theodoric Borgognoi of Lucca (bishop of Cervia) was interacting with Hugh of Lucca, Jean Piticard of Paris, and Lanfranc of Milan. Another cleric who obtained degrees in theology, philosophy and medicine from Montpellier and Paris was Henri de Mondeville. He became a military surgeon for King Phillip in 1301 and joined the faculty at Montpellier by 1304 [32]. There is only one image of de Mondeville and he is teaching pupils in an illustrated pre-printing press manuscript (Fig. 18.1a) [33]. There are only 18 known copies of his magnum opus *The Anatomy* which he began to write in 1305 spending 14 years on it, finishing in 1320 [34]. Now anyone can read de Mondeville thanks to the efforts of Leonard D. Rosenman from U.C. San Francisco translated his entire corpus [35]. Henri's days were filled with seeing patients at court and teaching. He devised the first known anatomical teaching charts, he promoted a sense of professional dignity amongst surgeons, and he even discusses methods to determine surgical fees (Fig. 18.1b). Henri inherited Theodoric's belief that suppuration of wounds was not beneficial to healing. He practiced cleanliness, debridement and prompt suturing of wounds. He tried to avoid placing irritants in contact with his incisions. He invented his own forceps, needle drivers, and a magnet to extract metal foreign bodies. "*Let the surgeon take care to regulate the whole regimen of the patient's life for joy and happiness by promising that he will soon be well, by allowing his relatives and special friends to cheer him and by having someone tell him jokes, and let him be solaced also by music on the viol or psaltery. The surgeon*

Fig. 18.1 (**a**) Only known image of Henri de Mondeville, (**b**) the rare illustrations he utilized to teach surgery, (**c**) Guilhelmus Fabricius Hildanus (1560–1634), (**d**) Frère Jacques Beaulieu (1651–)

must forbid anger, hatred, and sadness in the patient, and remind him that the body grows fat from joy and thin from sadness" [35]. This is rather a modern notion, more Oslerian than a Middle Ages conception from a surgeon. One final quote of Henri's should be presented, "*Surgery cures more complicated maladies, such as toward which medicine is helpless. Surgery cures diseases that cannot be cured by any other means, not by themselves, not by nature, nor by medicine. Medicine indeed never cures a disease so evidently that one could say the cure is due to medicine*" [35]. Spoken like a true surgeon.

The Sixteenth Century

Giovanni De Romanis was a lithotomist who trained his pupil Mariano Santo or Sanctus in the ancient art of perineal lithotomy probably in Rome. Marianus in turn taught the world about the technique that probably was originated by his master by publishing his work *Libellus Aurues de lapide a vesica per incisionem extrahendo* in 1522 [36]. Mariano was born in Barletta in 1488 and he probably died in Rome about 1565. Around 1510 while he was in Rome he studied medicine and surgery under his master, Giovanni de Vigo (1460–1525). He also worked with Giovanni De Romanis from Casalmaggiore and Givanni Antracino from Macerata [36]. He finally finished his degree in medicine at the hospital of Santa Maria dell Consolazione and remained as a teacher there until 1516. He took his degree between 1521 or 1522 and his name was inscribed at the Noble College of Physicians. He published a compendium of Giovanni da Vigo's *Practica copiosa* that same year as well as what he became most famous for, the *Libellus Aurues* [36]. He returned to Barletta because of his father's death and was called to Milan to serve the powerful Trivulzio family. He followed the family to Ragusa and as a military surgeon during the war against the Turks. Here he met Guido Randoni to whom he dedicated the second edition of his book in 1535 from Venice. He remained in Venice and published another work in 1542 a commentary on Avicenna for the use of surgeons. We do know that he eventually went back to Barletta and that he had two sons, Giamaolo and Cesare but there is nothing further that is known of Sanctus. De Romani was apparently worried that divulging the new technique would do more harm than good because he worried that ignorant and presumptuous men would pick up the methods and patients would suffer. It was Marianus who thought that the modern notion of teaching would help perpetuate the ideas themselves [36].

Marianus in the opening paragraphs gives praise to the Ancient Greeks, "*Therefore we ought to thank them very much for having shown us the way, even though it be winding, steep and bumpy, to accomplish such a difficult enterprise*.

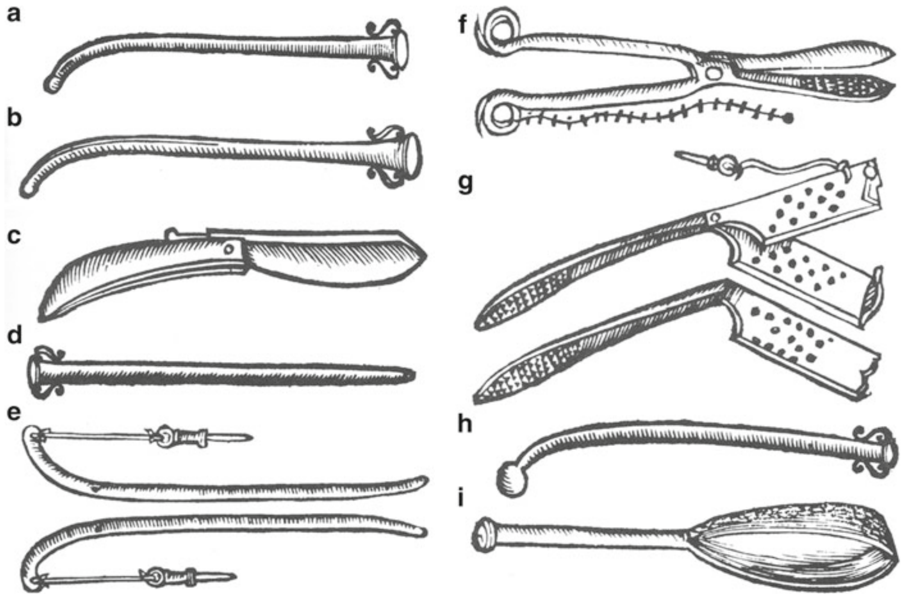

Fig. 18.2 The lithotomy instruments of Giovanni De Romanis used by Mariano Santo and illustrated in his 1535 work *Libellus Aureus*. (**a**) Probing syringe, (**b**) Itinerary, (**c**) Razor, (**d**) Explorer (dilator not shown), (**e**) Guides, (**f**) Pincers, (**g**) Laterals, (**h**) Conveyor (button), (**I**) Cleaner (spoon)

And I think all this happened owing to the difficulty of the matter, if one considers that Hippocrates himself often tried to perform this operation and having disappointed, he wrote in his "Oath": "I will not use the knife, not even on suffers from the stone; but I will give place to such as have skill in this art", as if he despaired of succeeding. Indeed it almost seems here as if he were inspired by a prophetic spirit and was predicting the arrival of my master Ioannes de Romanis of Cremona (this because, before saying ought else, it is my custom to praise my master, for everything I learned) who taught me this art" [37].

The whole first portion of his text is on the theories of four humors and timing of surgery based upon astrology. But he gets to the instruments necessary for performing this new method of lithotomy. We will present them in order (Fig. 18.2). (1) The probing syringe or the pipe (Fig. 18.2a). "*It is thirteen inches in length and is round and canalized like a pipe*." The tip is slightly curved and it can be used to "*inspect the bladder in greater depth and fish out the stone*." (2) The itinerary is a second pipe with a groove on the concave side (Fig. 18.2b). "*Its name is Itinerary because the incision must be made upon it, which depending on the extent to which we insert it into the bladder, allows us to identify the neck of the bladder with precision*." (3) The razor, like that used from a barber (Fig. 18.2c), but "*thinner and shorter so that it may no weigh on the hands of the surgeon*." It needs to be sharp to cut with one stroke the groove of the Itinerary. "*Indeed, if we cut with a sawing motion we irritate Nature greatly, when it ought to be disturbed as little as possible, otherwise no medicine will soothe it thereafter*." (4) The explorer (Fig. 18.2d), "*is a silver pipe also called the 'way' because it enters the incision reaching the groove in the convex side and following to the head, which is already inside of the bladder*." (5) Two guides, "some call the stylus" are made of silver with curved ends which are inserted next (Fig. 18.2e). (6) The dilator looks like a scissors that opens the wound gently spreading the instrument (Fig. 18.2f). (7) The pincers are saw-toothed graspers that can reach into the bladder and extract the calculus (Fig. 18.2g). (8) Two laterals, are hammered pieces of steel with holes with the sharp points inwards to grasp a stone that is very large for extraction (Fig. 18.2h). (9) The lithotrite, he skips purposefully because of the dangers involved in breaking stones. (10) The conveyor or button is made out of silver with a ball not larger than a cherry to explore the bladder at completion to insure that there are no remaining stones or fragments (Fig. 18.2i). (11) The cleaner or spoon is used last, this removes and catches anything that the conveyor brings up out of the bladder (Fig. 18.2j) [37].

Marianus concludes with some pithy remarks about further education and training. "*But knowledge (in my view) springs from observing a master while he is performing a surgical operation and memorizing and keeping well in mind what looks worth remembering, so that when, some day or other, they want to operate it may seem that they are operating in the presence of their master. So they will succeed in every operation, because it would be impossible to bring this operation to a successful conclusion in a different way, especially if one does not know the instruments. Indeed we see that not only a craftsman but Nature herself lies idle when suitable instruments for work are missing, and this happen chiefly when the sensibilities are dull*" [37]. So Marianus Sanctus immortalized his master Giovanni de Romanis and moving surgery into an art that required multiple and well thought out instruments. This would be the operation of the "greater apparatus" differentiating from Celsus's "*lesser apparatus*." Surgery would not have to wait nearly as long for the next revolution, the lateral lithotomy of Frère Jacques. It is a fitting end to this portion to once again quote Sanctus about his master in the final portion of his surgical description. "*A sure and complete extraction has been performed when all this has been done in the stages that my master Ioannes de Romanis of Casalmaggiore near Cremona, who lives in Rome, followed and often follows. A man whom almost all envy, because they have practiced surgery for ages without ever acquiring this new and sure art of extracting the stone, which he invented only by following Nature*" [37].

Pierre Franco was a barber-surgeon who grew up in the Provence region at Turriers, his birth date is not known, but has been estimated in 1505 or 1506. He did not come from a wealthy family and he references being apprenticed to a hernia surgeon and we know nothing about much of his career. He taught anatomy and surgery at Freiburg and Lausanne. He published a small treatise in 1556 (Petit Traité) and a larger volume in 1561 (Traité des Hernies) [38]. (Petit Traité contenant une des parties principales de Chirurgie laquelle les Chirurguns Herniaires exerecent.) It is in these texts that he states that he has practiced for 30 years. We also learn that he had strong Calvinist leanings making him a Huguenot and he was forced to flee France for Lausanne. Franco's first treatise was 144 pages in length with 16 fairly primitive woodcut illustrations [38]. It was small, duodecimo and was published in France by Antoine Vincent and is rare piece of incunabula. It was reproduced in 1881 by Professor Albert from Innsbruck. In this work Franco confined himself to a general discussion of surgical practice. His second book was much more ambitious and he published this one in Lyons by Thilbauld Payan. This work was 554 pages with 39 illustrations. In Book II Franco begins his discussion of stone disease and Chapter 27 he describes the use of catheters and sounds [39]. It is towards the end of this section that he describes a trick for removing difficult urethral stones. "*Gently milk it with your fingers as far as possible, even to deliver it. Help with fomentations of herbs*." Now the coup de grâs, "*If you cannot milk the stone all the way out, I suggest that you call on somebody to suck it out. I have used that method several times with success*" [39]. Paré often used portions of Franco's writings in his own works, but he does not use or reference Franco's suck technique. Malgaigne, a surgical commentator alluded to this technique as "*absurd and disgusting*" [39]. The last known reference to it was in G.M. de a Motte in his 1771 La Chirurgie [40].

Franco left a more significant legacy for bladder stone surgery because he also described the first elective suprapubic vesicolithotomy. He published the history of his case of the high operation in his works. (Traité des hernies contenant une ample declaration de toutes leurs espéces, et autres excellentes parties de la chirugie, assavoir de la Pierre, des Cataractes des yeux, et autres maladies, desquelles comme la cure est périllieuse, aussi est-elle de peu d'hommes blen exercée: Avec leurs causes, signes, accidens anatomie des parties affectes et leur entiére guarison: par Pierre Franco de Turrier en Provence, demeurant à Orenge.) He resorted to the high operation because he the patient, a two year old boy was suffering extreme agony; he had made the lateral incision and could not extract the stone because of its great size, the size of a hen's egg. "*The parents desired that he should die rather than continue to live in such miser; and I, too, wished to avoid being reproached for not having been able to extract the stone, (which was great folly on my part) &c.: yet I do not advise any one to do the like*" [39]. This was close to 1556.

One final notable who contributed significantly to all aspects of surgery for bladder stones was Guilhelmus Fabricius Hildanus (1560–1634). He was born at Hilden on June 25, 1560 [41]. He was a scholarly youth, but his education was cut short by an early paternal death and he contracted bubonic plague and was ill for 6 months. He apprenticed with a surgeon named Cosmas Slotanus who was trained by Vesalius at Padua. Hildanus was impressed by the necessity of knowledge of anatomy (Fig. 18.1c). In addition, Hildanus picked up medicine from Reinerus Soleander and Galen Wierus in Düsseldorf at the court of the Duke of Cleve. Hildanus learned to keep detailed case records and Wierus probably passed on his antagonism of the mysticism of medicine. After the death of his master Slotanus, Hildanus became a travelling surgeon [41]. In 1585 he was working in Geneva with Johann Griffon and they did much dissection. He married Marie Colinet while in Geneva, who was the daughter of a printer and a surgeon and midwife for women. She became Hildanus's principle assistant. She developed a powerful magnetic device for extracting metal from the eye. Hildanus mentions that his wife was his colleague but never neglected the home or their eight children [41]. They moved again in 1588 and again in 1591 arriving in Cologne. Here he published his first book *De Gangraena et Sphacelo* [41]. In 1595 the family was back in Switzerland first in Geneva and then on to Lausanne. By 1598 they were back in Cologne and he published his *Observtionum et curationum chirurgicarum* (25 carefully documented case histories) [41]. He again returned to Switzerland and eventually spent 9 years in the small town of Payerne (Peterlingen) near Lake Neuchatel. He practiced with increasing fame but continued to publish. He wrote a treatise on Dysentery in 1606 and his *Observation and Surgical Cures* in 1606. His family and the community suffered from the plague in 1612 and he finally moved to Berne in 1614 where they remained for the rest of his life. Of his many writings, only three have been translated into English and *Lithotomia Vesicae* was one of these [42].

He first published *Lithotomia Vesicae* in Basel in 1626 and it was quickly translated into Latin by his pupil, Henry Schobingerus who published this from Basel in 1628. John Norton in London was so impressed by the "*accurate account of the stone in the bladder, its causes, diagnostic signs and in particular the method of extraction both in men and women*" that he translated the text into English in 1640 [43]. This book contained 27 chapters that dealt with all aspects of urinary calculi. In the first chapter Hildanus he references the great authors of antiquity about stones including: Hippocrates, Galen, Avicenna, Celsus, Albucasis, Lanfranco, Guy de Chauliac, Vigo, Vesalius, Fallopius, Fabricius ab Aquapendente and Abroise Paré. He notes that stones were "*a preternatural, gross, slimy, coagulated humour, broght into a stone of thick matter by a preternatural heat and hidden quality of the bladder*." He spends some time discussing lithotomy instruments. He states there "*should be plenty of instruments made from the best iron*" [43]. Hildanus discusses five methods of lithotomy, the first was the method of Celsus. The second was that of Sanctus using what he called itenerarium, conductor and hamulus. The third was also described by Sanctus and Paré that was similar but used pincers for grasping and extracting the stone. The fourth method was the described by Franco where a suprapubic incision was made down to the ineneraium and a "*tent*" is left in the wound to suppurate and within a few days the stone will either pass or can be extracted with forceps. The fifth method was also from Franco, the most dangerous, where a suprapubic incision was made into "*the inguen above the upper part of the os pubis*" and he mentions the dangers of this approach [43]. He also was a proponent of keeping the wounds open to drain with "tents" for the urinary tract to heal, he would use silver cannulas to drain the urine [44].

The Seventeenth and Eighteenth Centuries

If one were to generate a lineage of lithotomy legacy it could read something like Giovanni Romoni taught Mariano Santo de Burletta (Marianus Sanctus) who taught Octaviano de Villa of Rome who taught Laurent Collot. After the death of Octaviano and at the beginning of the sixteenth century Henri II of France asked Laurent Collot to come to Paris as the Royal Operator and the family legacy began. The Collot family of barber-surgeons actually evolved into something much more than barber-surgeons, they evolved the instruments for surgical procedures as well. They were a closed knit family who were capable of keeping the secrets of their successful craft until Francois Colot published his posthumous Traité de l'Operation de la Taille (Treatise on the Operation of Cutting. 1717) [45]. There were rumors of their secret methods, and some believe that other surgeons actually drilled holes in the ceiling to spy on the family's secret methods of lithotomy [46]. Germain Colot might have been the surgeon who operated upon the famous case of the Archer of Meudon, after appeals to Louis XI in 1474 [47].

One of the most intriguing figures in all of medicine is Jacques Beaulieu. He was born in 1651 at a small rural village in France, Langsonnière in the Burgundy region. That he was ambitious is beyond question, he served in a cavalry regiment as an assistant surgeon where he worked for 5 years. He apparently learned the ancient art of lithotomy before carrying on by himself in Provence and Marseilles. John Bell the great Scottish surgeon wrote on the first biographies of Frere Jacques sums his phenomenal rise as follows, "*Imagine it, when in the Hôtel Dieu, where, for centuries, nothing had been exhibited but the lingering cruelties of the apparatus major, where professed lithotomists laboured for hours amid, the outcries of the patient to extract the stone, an operator appeared, daring beyond all belief, making light of that operation which had been regarded as the masterpiece of surgery, who, without hesitation or fear, performed by incision what had hitherto been attempted only by force of repeated dilations! Who boldly plunged his dagger-pointed knife into the hip, thrust it home into the bladder, felt for it with the staff, then enlarged his incision upwards and downwards, and in a few moments extracted the largest stone*" [48]. He literally exploded onto the center of surgery in all of Europe, Paris as an unheralded itinerant surgeon, with no credentials and no formal training (Fig. 18.3a). His technique was rough hewn, with very little true anatomical knowledge but he appears to have had what surgeons always must have, fierce belief in their capacity to do good Bessière was one of the leading surgeons in Paris watched Beaulieu perform 60 consecutive lithotomies and described the scene which we'll quote now in detail:

> "*He laid his patients upon the operating table, and, placing a pillow under his head, gave him to the assistants to hold, with the thighs elevated and the heels bent towards the buttocks. He never tied his patients. He made use of a steel staff shorter from the handle to the heel, where it bends more than ours, and he had but two, one for women, one for men. He introduced his staff (big, round and having no groove) into the bladder, and, holding it with the left hand, he pressed it so against the perineum as to make that part of the bladder project which he meant to strike with the knife. Then, taking in his right hand a long knife, dagger shaped, he plunged it into the left hip at the distance of two inches from the perineum and pushing it directly onwards, opened the body of the bladder as near as possible to its neck, never once withdrawing the bistoury till he had made an opening proportioned to the size of the stone, which he then introduced his finger to feel for and running in a conductor along with the finger he introduced the*

Fig. 18.3 (**a**) Frere Jacques Beaulieu, (**b**) Burrough on the Hill by Cheselden's friend Dr. William Stukeley (1687–1765), (**c**) William Cheselden's portrait by Jonathan Richardson, friend and neighbor

> *forceps upon it, seized the stone, pulled it coarsely out, indifferent to the effects of that violence with which it was extracted…contents himself with a little oil and wine for a dressing and when once remonstrated with for his want of after care said, 'I have extracted the stone, God will cure him.*'" [48]

There were plenty of witness who watched with awe as Beaulieu performed his miraculous new operation. Dionis who was an anatomist and surgeon of Marie Therese of Austria was present and confirmed Bessière's account. Martin Lister from England, also an anatomist wrote a commentary on Beaulieu's dexterity. "*He cut both by the small and the great apparatus and in both boldly thrusts a broad lancet or stiletto into the middle of the muscles of the thigh near the anus and plunges it till it meets the staff or the stone. I saw him perform the operation upon nine persons in three-quarters of an hour. Very dexterously he seemed to venture it all and put me in some disorder, and a stouter Englishman than myself with the cruelty of his operation. However, I visited them all in their beds and found them more amazed than in pain*" [49]. Mery apparently at first drew up a rather fair report of Jacques' performance, but the lithotomists were not to be satisfied with this and wanted to concentrate on his failures and complications. They were also astounded and more than a bit put off by the fact that Jacques did not want either money or fame, but believed that his gift came from God and needed to be used. He was ousted from Hôtel Dieu and proceeded to the Court at Fontainbleau became acquainted with Duchesne, the first physician to the princess. He was introduced to Fagon and Felix the physician and surgeon to Louis XIV. He again performed six lithotomies and they were all notably impressed. De Harley, his initial sponsor from the French Parliament was convinced again by these Royal physicians was sent a second time to the Hôtel Dieu to the great consternation of the surgeons. By now, the sensation of this simple man, in monkish garb who desired no wealth became the talk of all of Paris [48]. On the 7th of April, 1698, the magistrates, physicians and surgeons gathered at the Archbishop's palace and Mery weighed in favor of excluding Frere Jacques, but this was over-ruled in favor his operating again at the hospital. His enemies were now fully aligned against him during his second tenure where now guards and sentries had to be posted to prevent the throngs of crowds from flooding into the place to observe the friar. It was as if fate intervened against Jacques at this moment because 25 our his next 62 patients died when he operated at La Charité but the disenfranchised Jacques blamed the careless postoperative care of the monks as part of the cause of his high mortality rate. But a large number of deaths also occurred at the Hôtel Dieu and the thundering vitriol by the surgeon Marechal drove Frere Jacque from Paris [48].

He showed up 1 year later as the lithotomist to the King of Holland. Again dissention amongst the ruling physicians and surgeons rose up to appose the work of Jacques. But Rau observed the technique of Jacques carefully and being an astute anatomist, corrected minor flaws of Jacques and developed his own secret method of lateral lithotomy after Frere Jacques had been successfully ousted from Holland by the physicians and surgeons. Rau in the meantime gained a considerable reputation as to the superiority of his new method of lithotomy but could not be persuaded to divulge his method, even to his own pupil, Albinus. Albinus in turn did try to help Cheselden in England, but literally Cheselden had to learn the anatomy and the surgical approach by himself. Bell stated "*he had no guide save the descriptions of Albinus, who, though himself a pupil of Rau, was himself deceived*" [48]. But the guide was always Frere Jacques, not Rau. Jacques returned once again to Amsterdam in 1704 and Bell relates "*Rau, whose rare talents and incomparable meanness of disposition kept an almost equal pace, so that we know not whether most to admire or detest the man, published, like Mery, his daily scandals, dissected Frere Jacques out of the capital, yet stole the very operation which he affected to condemn*" [48]. And what of Rau, did he defend his actions in any way? In his course of Operative Surgery regarding lithotomy he states "*that he had nothing to say upon that head, because it was the means by which he got his living; and I had rather be silent than propose any thing that might mislead you from the truth: but, if you can learn it by seeing me perform it upon living subjects, you are welcome; and for the rest, you may read Celsus*" [48].

Frere Jacques operated in all, three times in Paris and failed to convince the established surgeons the superiority of his lateral method of approach for perineal lithotomy. The third and final time is perhaps the saddest. Fagon, the physician to the King recalled Jacques in about 1700 because he too suffered from bladder stones. Fagon could have chosen Marechal, the leading lithotomist in Paris and outspoken antagonist to Jacques, but he chose Frere Jacques. Jacques returned to Fontainbleau and Fagon began to teach Jacque anatomy on the cadaver. Duvernet a celebrated anatomist was called in to aid in the dissections and teaching. Felix too was assigned to discuss physiology and the harm that could be caused by injury. Finally, they encouraged that Jacques use a grooved sound and had Jacques perform about 38 lithotomies in Strasburg with his newly acquired knowledge and only one fatality. A nobleman named Maréchal de Larges also suffered from bladder stone and had 22 poor patients arranged to test Jacques and his new technique. All did well and de Larges then submitted himself to the operation, he died the next day of an excruciatingly painful injury to the rectum. Unfortunately for Jacques, Fagon changed his mind and Maréchal operated on his stone at Hôtel Dieu and Jacques left Paris for the last time [48]. He taught his technique to Rau in Amsterdam, but Rau refused to help Jacques and in fact, probably aided the forces that drove him from the Netherlands. Jacques went on through Germany where the famous surgeon Heister observed him operate and was much impressed with his methods. Jacques continued with success outside of major surgical centers such as Paris and Amsterdam, operating for about 30 years. Some have estimated that he performed over 5,000 lithotomies before he died at 68 years of age back in France. He gave away to the poor of the communities where he visited and was usually received warmly by communities. The nursery rhyme "Frère Jacques" refers to a Jacobinic monk who often oversleeps, and there is nothing in the rhymes about this lithotomist [50].

Claude-Nicolas Le Cat (1700–1768) was born in Picardy and studied anatomy and surgery in Paris. He was appointed surgeon to the Archbishop of Rouen in 1726 and eventually as head surgeon at the Hôtel Dieu in Rouen [51]. He performed a large number of lithotomies and invented many of his own instruments. He was passionately interested in anatomy and strove to develop an anatomical simulator that he could train others to perform surgeries, such as lithotomy. We also know that he was also envious of any successes that trumped his own, this lead to the great rivalry with Baseilhac. Morand would later report on the mortality rate in these years at the Hôpital La Charité as follows [52]:

Year	Number cut	Deaths
1731	14	8
1732	11	4
1733	16	8
1734	17	9
1735	13	9
Total	71	38

Jean Baseilhac (1703–1781) was from a long line of surgeons, born in Hautes Pyrénées. His father, grandfather, and uncles were all surgeons at the Hôtel Dieu in Lyons. The young Jean trained with his father in 1724 and he left to go to Paris by 1726. It was in Paris that Jean Baseilhac became more involved with the Church and he was talented enough to get a serious patron in Prince Francois Armand of Lorraine [53]. In 1729 he became Frère Jean de St. Côme. He was always restlessly trying to improve both his skill and the instruments for performing surgery. He became a full priest in 1740 but was given special dispensation to practice surgery on the poor full time. He studied the methods of injury by the instruments and in 1748 he tried his "*lithotome cache*" which consisted of a slotted curved blade in a spring-loaded handle [54]. The slot concealed the knife until the cut was ready to be made and could be adjusted for size on the handle. This might well be the first true precision instrument in surgery and he would eliminate the use of the gorget with this recessed knife [55]. With this device, he could cut the vesical neck and prostate to any size he desired based on the size of the calculus. Le Cat was his primary antagonist from his position at the Hôtel Dieu. This battle would last over 20 years between these two gifted lithotomists. Côme's reputation and practice steadily grew and in 1753 he was able to establish his own hospital near the Rue St. Honoré. He also became interested in the "high operation" for the stone and developed special instruments for that approach which he increasingly favored [53].

William Cheselden

We've already presented William Cheselden (1688–1752) in some detail, but since he is a towering figure in the history of urolithiasis some further comments are necessary. He was born on October 26, 1688 in Burrough on the Hill north of Leicester to George and Deborah Cheselden [56]. Later in life, a friend of his William Stukeley, M.D. made a drawing of the home writing beneath it "*Will Cheselden Chirurgo peritissimo, Amico*" (Fig. 18.3b). William was the third child and second son and he received a good primary education at the Wyggeston School. It is probably that through the influence of a distant relative, Dr. George Cheselden that he became interested in medicine/surgery and he signed an apprenticeship with James Ferne in London at age 15. He paid £200–£300 per year to his master [57]. He probably learned his anatomy from William Cowper who had become quite famous for this work. He never lost his interests in this subject throughout his long career. It was during his second year of apprenticeship, that Ferne was appointed to cut for the stone at St. Thomas's Hospital and Cheselden would have been one of his assistants. He finished his training on December 5, 1710 and was made free by the Barber-Surgeons' Company [57]. As all young surgeons of his day, he now had to earn his living, but had no hospital in which to practice. Cheselden drew up a syllabus of lectures for anatomy which he published at Stationers' Hall on October 8, 1711. The syllabus included 35 lectures of about 80 pages that served in his teaching for the next 25 years [57]. It appears that his anatomy lectures and course were successful and he possibly taught the course at a house in Cheapside. He taught the course for at least 2 years; before he was elected a Fellow of the Royal Society in 1712 (Fig. 18.3c). He published his *The Anatomy of the Humane Body* in 1713 and it became a popular text [58]. Cheselden was never considered a great writer, but his textbook of anatomy was short, concise and applicable to surgeons and therefore became quite popular.

Table 18.1 The editions of Cheselden's *The Anatomy of the Humane Body*

First edition	1713	Seventh edition	1750
Second edition	1722	Eighth edition	1763
Third edition	1726	Ninth edition	1768
Fourth edition	1730	Tenth edition	1773
Fifth edition	1740	Eleventh edition	1778
Sixth edition	1741	Twelfth edition	1783
		Thirteenth edition	1792 (last)

Table 18.1 is the running history of the textbook's editions showing its longevity in an era where new anatomical findings were the norm [59]. In the first edition he states in the preface "*This treatise being deisgn'd for the use of those who study Anatomy for their entertainment, or to qualify themselves for the knowledge of physic or surgery, and not for such as would be critically knowing in the minute parts etc*." [58] He also acknowledges the assistance of another anatomist who would later develop a significant relationship throughout his lifetime, Dr. James Douglas. "*It is with great pleasure I here acknowledge my obligations to Dr. Douglas, that most accurate and indefatigable anatomist whose assistance has been very useful to me in the compilation of this work*" [58]. The Douglas brothers, James and John would figure prominently and not altogether warmly in William's future writings. Finally, it is worth noting that Cheselden made significant alterations up until the sixth edition, thereafter he did little or no alterations of the text or illustrations [59].

Cheselden married Deborah Knight the same year as his textbook was released in 1713. They had a daughter the following year that they also named Deborah. He applied for a position at St. Thomas's and failed in 1714 and a more ominous event followed when the Court of Assistants of the Barber-Surgeons' Company was sanctioned for his anatomy classes. Cope presents the details of this action and it most likely started his lifelong desire to separate the surgeons from the barbers because of the latter's inability to appreciate the crucial importance of anatomy, anatomical dissection and research [59]. But despite the censor of the Barber-Surgeons' Company he continued his successful anatomy classes and a second daughter, Williamina was born in 1716. At the age of 30, he was finally chosen as the Assistant Surgeon at St. Thomas's on July 9, 1718 and he and his family moved from Cheapside to Red Lyon Street close to his friend Richard Mead. During his early tenure at St. Thomas's Hospital he developed a reputation as a skilled surgeon and a great teacher, but he also famously operated on Mrs. Margaret White who had an umbilical hernia with necrotic bowel. He was able to resect the necrotic segment but she was left with a colostomy which she was able to live with for many years [59].

As a new staff surgeon he would not be allowed to perform lithotomy until this operation was appointed to him (Fig. 18.4a). He certainly could have performed this surgery for private patients in their homes from 1718 till 1720. From 1720 until 1722 he would have utilized the Marian operation. In 1722 however he began to experiment with the suprapubic or high operation for the stone. We will go through this phase of his career with his writings on this subject later in the chapter. But by August of 1725 he had modified Frére Jacques lateral lithotomy technique and began to introduce the anatomical ramifications for this method of surgery (Fig. 18.4b) [59]. We have an inclination of Cheselden's hopes for this new operation in this following statement, "*Hearing of the great success of Mr. Rau, professor of anatomy at Leyden, I determined to try, though not in his manner, to cut directly into the bladder; and as his operation was an improvement on Friar Jacques, I endeavored to improve upon him by filling the bladder as Douglas had done in the high way, with water, leaving the catheter in, and then cutting on the outside of the catheter into the bladder in the same place as upon the gripe, which I could do very readily and take out a stone of any size with more ease than in any other way*" [59]. His new technique proved to be rapidly superior. James Douglas wrote an account of the operation with details in 1726 (see Addendum) and further commented "*This is Mr. Cheselden's regular method of Cutting; and when no accident happens, which it was impossible to be aware of before the operation, he has*

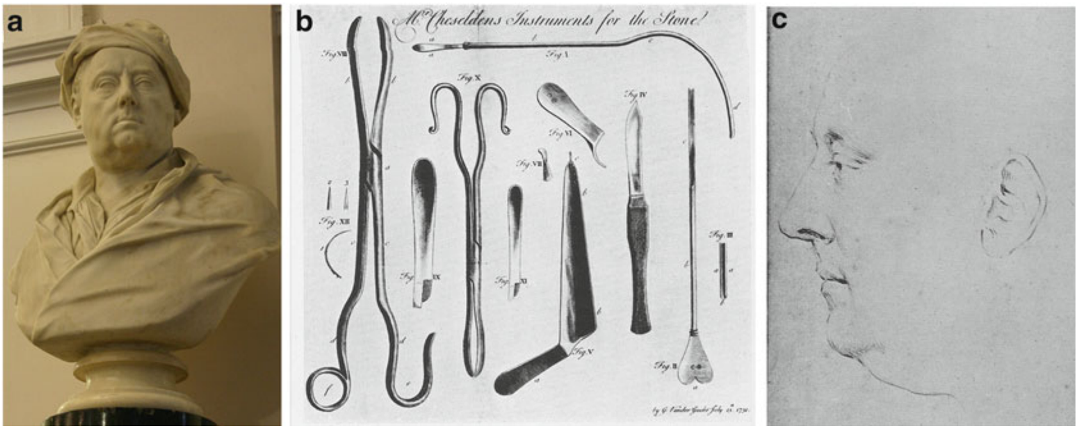

Fig. 18.4 (**a**) Cheselden bust by Roubilliac, (**b**) Cheselden's lithotomy set, (**c**) Cheselden's self-portrait

seldom been above a minute (sometimes less) between the beginning of the first incision and extraction of the stone" [59]. In fact, James Douglas further comments on the methods employed by Mr. Cheselden prior to trying his new operation upon living patients [58]. "*And I most willingly embrace this opportunity of doing justice to the ingenious Dr. Bamber and Mr. Cheselden, by declaring in a publick manner (what I had many opportunities of knowing, having assisted at most of the experiments they made on dead bodies) that as it was their turn to cut in the two great Hospitals of this City the following season; I beheld with the utmost pleasure the alacrity, industry and application with which they soon made themselves masters, each in the way that suited his genius best of the true method of performing an operation which they thought they had all the reason that theory could furnish, to prefer even to the high way of cutting, which both of them had for a considerable time practiced with great success*" [59]. He modified his technique yet again after his first eight cases and the Cheselden method became the standard for the next 150 years (Table 18.2).

Cheselden humbly presented his own outcomes in the later additions of his *Anatomy* and we will let him tell the tale himself:

> "*What success I have had in my private practice I have kept no account of because I had no intention to publish it, that not being sufficiently witnessed. Publickly in St. Thomas's Hospital I have cut two hundred and thirteen; of the first fifty only three died; of the second fifty, three; of the third fifty, eight; and of the last sixty three, six. Several of these patients had the small-pox in their cure, some of whom died, but I think not more in proportion that what usually die of distemper; these are not reckoned among those who died of the operation. The reason why so few died in the two first fifties was, at that time few very bad cases offered; in the third, the operation being in high request, even the most aged and most miserable cases expected to be saved by it; besides, at that time, I made the operation lower in hopes of improving it, but found I was mistaken. But what is of most consequence to be known is the ages of those who recovered and those who died; between ten and twenty, sixty two cut, four died; twenty and thirty, twelve cut, three died; thirty and forty, ten cut, two died; forty and fifty, ten cut, two died; fifty and sixty, seven cut, four died; sixty and seventy, five cut, one died; between seventy and eighty, two cut, one died. Of those who recovered the three biggest stones were twelve ounces, ten and a quarter ounces and eight ounces, and the greatest number of stones in one person was thirty three. One of the three that died out of the hundred and five was very ill with whooping cough, another bled to death by an artery into his bladder, it being very hot weather at that time: But this accident taught me afterwards, whenever a vessel bled that I could not find, to dilate the wound with a knife, till I could see it*" [59].

The Norwich School of Lithotomy

We have discussed the Norwich School of Lithotomy in some detail already. We have looked at the surgeons (Table 18.3), beginning

Table 18.2 Eighteenth and nineteenth century lithotomists by country

	Eighteenth century		Nineteenth century	
French	Baseilhac, Jean (Frère Côme)	1703–1781	Larrey, Dominique	1766–1842
	Le Cat, Claude Nicolas	1700–1768	Duypuytren, G	1777–1835
	Ledran, Francois	1685–1770	Civiae, Jean	1792–1867
	De Lafaye, Georges	?–1781	Souberbielle, J	1754–1846
	Louis, Antoine	1723–1792	Sanson, Louis J	1790–1841
English	Bromfield, William	1712–1792	Cline	
	Cheselden, William	1668–1752	Cooper, Astley	1768–1841
	Sharp, Samuel	1700–1778	Carpue, Constan	1764–1846
	Hawkins, Caesar	1711–1786	Thompson, Henry	1820–1904
	Norwich School of Lithotomy	1772–		–1902
Italian	Alghisi, Tommaso	1669–1770	Scarpa, Antonio	1752–1832
	Bertrandi, Ambrogio	1723–1765	Vaccà-Berlinghieri	1772–1826
	Pallucci, Guiseppe	1716–1797		
Netherlands	Rau, Johann Jacob	1668–1719		
	Ruysch, Frederik	1638–1731		
	Albinis, Bernhad S	1653–1721		
German	Hildanus, GF	1560–1634	Kern, Vincenz	1760–1829
	Heister, Loren	1683–1758	von Dittel, L	1815–1898
			Zuckerkandl, O	1861–1921
			Tandler, Julius	1869–1936
American	Physic, Philip Syng	1768–1837	Dudley, Benjamin W	1785–1870
	McDowell, Ephraim	1771–1830	Albert, Edward	1841–1900

with Benjamin Gooch (1707/08–1776), a lithotomist and key member of the community who brought the institution into existence along with the Reverend Samuel Cooper (1740–1800) who was the uncle of Sir Astley Cooper [60]. The Norfolk and Norwich Hospital became one of the leading centers for lithotomy in the world and the first to take detailed histories and notes regarding the patients and their surgeries, the complications and mortality. Sir. Astley Cooper spoke of this institution in 1835 "*the degree of success which is considered most correct is that taken from the results of the cases at the Norfolk and Norwich Hospital*." [61] Alexander Marcet wrote about this institution in 1817 "*In my enquiries I have met with great disappointments… it will appear scarcely credible that in the larger hospitals in London, St. Bartholomew's, St. Thomas's, Guy's and the London Hospital, no regular or at least no ostensible records of the cases of lithotomy which occur in them should be preserved. It is with great pleasure, however, that I am enabled to mention one striking exception to this unaccountable oversight in public hospitals. The Norfolk and Norwich Infirmary in this and several other respects, stands as a model of regularity and good management*" [61]. Jean Civiale in Paris described "*labelle et riche collection de Norwich*" in 1863 [61]. Sir. Henry Thompson wrote also in 1863 called Norwich "*the most perfect and complete record, literally graven in stone, that the world possesses of calculous experience*" [61]. We have discussed the strange case of Dr. Henry Reeve whose brother suffered and eventually died of recurrent cystine bladder stones that William Hyde Wollaston examined as the second documented case of this rare stone type [61]. Reeve sadly died at the young age of

Table 18.3 Norwich school of lithotomy surgeons

Surgeon	Years	Number of operations
W. Donne	1772–1800	173
W. Palgrave	1772–1775	5
J. Alderson	1772–1791	69
E. Rigby	1790–1814	106
P.M. Martineau	1793–1828	149
E. Colman	1803–1812	44
W. Bond	1813–1826	45
W. Dalrymple	1815–1838	90
J.G. Crosse	1826–1849	52
H. Carter	1830	2
B.H. Norgate	1831–1857	57
J.G. Johnson	1838–1847	10
G.W.W. Firth	1849–1878	58
W.P. Nichols	1850–1872	75
A. Dalrymple	1852–	2
W. Cadge	1857–1895	240
T.W. Crosse	1858–1895	77
C. Williams	1873–1906	73
M. Beverley	1879–1892	21
S.H. Burton	1890–1904	57
H.S. Robinson	1890–1904	37
D.D. Day	1896–1909	16
Sir. H.A. Balance	1898–1909	14
E.W. Everett	1907–1909	6

34 with so much future potential. The Reeve collection, his letters, and his stone analysis have all disappeared, but were recorded by Sir Peter Eade in 1900.

We will list the surgeons who practiced lithotomy again at the Norwich School because their legacy and commitment to this disease was so significant. We have noted Edward Rigby (1747–1822) who came to Norwich at the age of 15 and apprenticed with David Martineau. He was appointed as assistant surgeon at the age of 24 and went on to obtain his medical degree. He served the hospital as physician and surgeon for 49 years performing 106 lithotomies [61]. Philip Meadows Martineau (1752–1829) joined Donne and Rigby at the hospital following in the footsteps of his father, also a lithotomist who trained Rigby, David Martineau. Martineau gained wide acclaim for his surgical technique. Astley Cooper mentioned that "*no surgeon in London, I am certain, can boast of similar success and in Paris he was spoken of as 'le lithotomiste le plus eminent et le plus heureux de son époque'*" [61]. Martineau performed 149 lithotomies with a mortality rate of only 12.5 % (or about 1/8) and he described his own modifications of Cheselden's technique [61]. William Dalrymple (1772–1847) joined Martineau after training at Guys' and St. Thomas's Hospitals under Astley Cooper and Henry Cline. He performed 90 lithotomies over his 27 year career as staff at the hospital. These men were conscientious and worried about the patients they were entrusted. Edward Copeman, a young house-surgeon reported that Dalrymple stated "*I have often heard him say that he was not able to sleep the night before he to perform a lithotomy; although in such cases his success was great.*" John Green Crosse (1790–1850) was appointed to the surgical staff in 1823 and often assisted Martineau at lithotomies (holding the staff). Crosse studied in London, Dublin and Paris prior to coming to Norwich [61]. He was awarded the Jacksonian Prize of the Royal College of Surgeons of England in 1833 for his essay "*The Formation, Constituents and Extraction of the Urinary Calculus*" [62]. Crosse included in his references over 2,700 publications which was a monumental task. He was elected a fellow in the Royal Society. The final surgeon of note will be William Cadge (1822–1903). He studied medicine at University College Hospital and became the assistant to Robert Liston. He returned to Norwich because of ill health in 1854 and was appointed to the staff. He gave a summary of the outcomes at the 1874 British Medical Association meeting and the Hunterian lecture before the Royal College of Surgeons of England in 1886 [63]. He performed 240 lithotomies at the hospital, the greatest number by any surgeon, and at least 144 private surgeries outside of the hospital [61].

Others followed in the tradition of the Norwich lithotomists. Though several types of surgery were employed throughout these years, most were Cheselden's modified lateral approach (about 75 %). We have also presented the work of John Yelloly (1774–1842) who employed the skills of Michael Faraday to aid in the more detailed analyses of the Norwich stones [64].

We have used substantively the work of A. Batty Shaw in outlining the significant contributions to history of the Norwich School in many details that are not readily available from any other source [65]. It is Shaw who presented the statistical data regarding the decline and fall of bladder stone disease in this district by 1902 as well as the rise of lithotrity that supplanted lithotomy. In 1936 Sir D'Arcy Power noted that the lateral lithotomy literally defined the successful surgeon. But by then, the big surgical procedures and the perineal route were becoming a subject of historical interest only [66].

The Suprapubic Lithotomy

Digressing back to the most controversial approach to bladder stones probably first described well by Pierre Franco is the open surgical approach for large or complex bladder stones that is used today, suprapubic lithotomy which has been called the "*high operation*" [67]. We have already discussed in some detail the founding contribution of Pierre Franco near 1561 when he desperately removed a hen's sized stone from a 2 year old in Lausanne. He is certainly credited by those who followed, especially William Cheselden [68]. In 1590 another French lithotomist, Rossetus also began recommending the suprapubic approach for bladder stones. There were other anecdotal cases, rather like that of Franco's that followed in the intervening 200 or so years later [67].

John Douglas, the brother of James whom we've already encountered studied his brother's well known anatomical preparations showing all of the parts of the pelvis that involved both the low perineal and the high suprapubic approaches to the human urinary bladder. James had demonstrated his famous specimens to the Royal Society in 1717–1718 [69]. John conceived an idea approaching the bladder suprapubically from studying these specimens. John Douglas performed four high operations for stone between December 12, 1719 and March 23, 1720. All but the third patient did well from the surgery and John Douglas offered his services to the Westminster Infirmary and he offered to instruct other surgeons in the new technique, but only Cheselden was interested in the methods. Douglas opined "*…instead of accepting it as I expected, they all rejected it with scorn, as derogatory to the characters of the cutters, except Mr. Cheselden, surgeon to St. Thomas's Hospital, who has always the Good of Mankind at Heart, than any little private views of his own*" [70]. John would forget these generous words when Mr. Cheselden would replace him at the Westminster Infirmary with his new lateral perineal method [57].

Cheselden not only learned Douglas's methods, he soon surpassed him in skill at performing this new method. He performed the first two operations by May 5, 1722 and all through the summer of that year he operated upon a total of nine patients with only one death [57]. The patient that died was quite ill and had pyonephrosis of the right kidney that he could do nothing for. Cheselden wrote up this in a *Treatise on the High Operation for Stone* in 1723 [68]. He wrote up the history of this operation and gave full credit to John Douglas for the revival of the suprapubic operation. He presented the work of Rosset, that of Hildanus, Tolet, Dionis, and Peter le Mercier. He dedicated his work to his friend Richard Mead as follows, "*The success of these operations being greatly owing to the encouragement you gave me, both by your presence and favourable opinion of my undertaking I beg leave to make this public acknowledgment of it and to subscribe myself, Sir, your most obedient and humble servant.—Will Cheselden*" [68]. He also included two cases of strangulated hernia in this book; one was Mrs. Margaret White with the bowel stoma which he illustrated nicely. In addition he included a stone that formed on a needle, one around a bodkin and a third surrounding a bullet from a soldier who was shot at the siege of Lille in 1714. John Douglas followed with his book called *Lithotomia Douglassiana* in 1723 [70]. Cheselden's remarks on the eve of the development of his most widely known success came with his Fourth Edition of his *Anatomy* which we will quote at length [71]:

> "*The next season, it being my turn in St Thomas's I resumed the high way, and cutting nine with success it came again in vogue; after that every*

lithotomist of both hospitals practiced it; but the peritoneum being often cut or burst, twice in my practice, though some of these recovered, and sometimes the bladder itself was burst from injecting too much water, which generally proved fatal in a day or two.- What the success of the several operations was I will not take the liberty to publish; but for my own, exclusive of the two before mentioned, I lost no more than one in seven, which is more than any one else that I know of could say; whereas in the old way, even at Paris, from a fair calculation of over 800 patients, it appears that near two in five died. And though this operation came into universal discredit, I must declare it my opinion, that it is much better than the old way to which they all returned, except myself, who would not have left the high way but for the hopes I had of a better."

Frère Côme (1703–1781) was another proponent of the "high operation" for the stone. He was innovative and did much basic research and instrument development before embarking on any clinical application. He knew that forced bladder distension on patient suffering from bladder stones was painful and dangerous. Côme came up with the idea of opening the bladder from a retrograde approach. He devised and constructed his "sonde á dard" which was a curved hollow metal catheter containing a concealed pointed stilette cutting on the linea alba. He next used a "*trochar bistoury*" with another concealed blade to follow the groove on his sonde á dard with a downward motion to enter the bladder. The stone was then removed by inserting forceps or fingers. He used to drain the bladder by inserting a gum catheter via a perineal urethrostomy. He published his *Nouvelle Méthode d'extraire la Pierre de la Vessie urinaire par dessous le Pubis* in 1779 [72]. Côme particularly thought it advantageous in women, who risked incontinence following the perineal methods, but rarely was associated with the high method.

Sir. Astley Cooper liked to try everything rarely performed a supra-pubic vesicolithotomy. He believed it should be "confined to those cases where there is a combination of large stone together with a grossly enlarged prostate." By 1850, Murray Humphry performed a suprapubic lithotomy on a boy age 14 and collected the world's literature and could find but 104 published cases. He noted fatal outcomes in 31 of these cases, making it indeed appear to be far riskier alternative. But time stands still for no man and as we shall see, the technology for bladder stone disease would surpass the open surgical treatment of enlarged prostates by the pioneering endeavors of endoscopic surgeons within the next century. Cooper's and Humphry's observations would fall to the bygone muses of history.

The Transrectal Lithotomy

At the dawn of the nineteenth century virtually every method of lithotomy had been tried, but it was time for one more approach. The rectum was only a "*stone's throw*" away from the bladder and it was inevitable that someone would purposely try the approach that was so feared as a complication from the perineal approach for centuries. It appears it might have been introduced by M.J. Chelius in experimentally in 1779 and performed in 1791. L.J. Sanson (1790–1841) was a pupil of G. Dupuytren like Jean Civiale. Dupuytren apparently performed this technique as well; reporting his work in 1829 [73]. He studied carefully some of the modifications of Dupuytren to avoid injury to the rectum, so he was intimately aware of the close proximity of the rectum to the bladder. Andrea Vaccà-Berlinghieri (1772–1862) practiced in Pisa and published his work on the transrectal method. An outspoken critic of the transrectal method was the anatomy and surgery professor of Pavia, Antonio Scarpa (1752–1832) [74]. The transrectal method consisted of splitting the anal sphincter, dividing the anterior wall of the rectum to gain access to the prostatic urethra. They would identify this portion with a probe placed transurethrally. Once opened, they would dilate the tract into the bladder. Sanson explored a method where he would open the rectum a bit higher and bypass the urethra and incise directly into the posterior wall of the bladder [74].

In 1828, a remarkable event took place at the Hôtel Dieu in Paris. Three surgeons each operated upon stone patients using their favorite approaches. G. Dupuytren made his transverse incision, G. Breschet used the lateral cut technique and L.J. Sanson performed a transrectal operation. The two perineal surgeons patients did much better than Sanson's patients but the numbers were small in each arm [74]. The operation declined in France following this trial, but in America Bauer and Sims in New York City performed a transrectal stone extraction in 1859 [75]. They did not divide the anal sphincter, using Sims's vaginal retractor they made a high rectal incision and entered the bladder above the prostate and seminal vesicles. The stone was extracted and the closed the bladder and rectum with 5–6 silver wires that were removed on the eighth post operative day. The patient survived and was discharged on the next day. It did not take long for major complications to be reported as well and Dupuytren lost three out of six patients with pelvic abscesses [76]. But lithotrity was already making substantial inroads into the bladder stone population and the morbidity and mortality were remarkably less than the lithotomists. After 1860, referred to as the "*third period*" of Sir Henry Thompson was the time of the lithotrity and these historical methods of lithotomy were doomed to the graveyard for historians [77].

The American Lithotomists

The M*ayflower* and the *Speedwell* landed to settle the Puritans at Plymouth on December 21, 1620 with 102 total settlers (90 passenger's from the *Mayflower* and 20 aboard the *Speedwell* included the crew). That first winter resulted in 45 deaths, and by November 1621 the *Fortune* arrived with 37 new settlers. The *Ann* and *Little James* arrived in 1623 with 96 more settlers. By 1627 there were listed 157 colonists which increased to 300 by 1630. In 1637 Dr. John Clark (1598–1664) arrived in the Colony with a degree from Edinburgh and trained to perform lithotomy [78]. Little is known about his activities in the Massachusetts Bay Colony but there is a painting of him from about 1664. In 1710, Dr. Zabdiel Boylston put an add in the *Boston Gazzette* advertising that he performed lithotomy. Sylvester Gardiner was a native of Rhode Island and studied medicine in Boston as an apprentice. He travelled to Europe and in Paris worked with Petit and Le Dran. In London he worked with Cheselden and learned his method of the lateral incision, prior to returning to Boston in 1731. He presented this work at a local medical society by 1741. His first patient was a 6 year old boy, named Joseph Baker. Gardiner commented "*for want of Skill and Discretion in the Operator this Surgery too frequently kills the patient in a few days or Weeks*." But Joseph survived and thrived [79]. By 1738 he had removed a large bladder stone from a 68 year old retired officer, Amos Turner. He survived but died a year later and an autopsy showed four more stones in his bladder [80]. Interestingly, Engel recounts the lawsuit that ensued over payment that might just be the first litigation over stone disease treatment in the United States [78].

John Hunter was a pupil of William Cheselden and he in turn had a profound impact upon the American school of surgery. He clearly influenced his pupil and father of American Lithotomy Philip Syng Physick (1768–1837). Physick was born in Philadelphia on July 7, 1768. His father Edmund was Keeper of the Great Seal and Receiver-General for the Colony of Pennsylvania and wanted his son to become a doctor. He worked with his maternal grandfather who was a silversmith and Philip would later use these skills to help him manufacture some of his own surgical instruments. He graduated from Pennsylvania University in 1785 at age 17 and he attended medical lectures under Adam Kuhn. Kuhn had been a student of Linnaeus and taught at the Pennsylvania Hospital. In November 1788 he and his father sailed to England and John Hunter agreed to work with Physick. There is a story about the first meeting, when Edmund asked Hunter which books his son should read, Hunter famously replied by taking them to the dissecting room, "*These are the books your son will read under my direction: the others are fit for very little!*" [81]. He became his assistant at St. George's Hospital in 1789 and Hunter references his once in his Treatise on the Blood, Inflammation, and Gun-shot Wounds. "*Many of these experiments were repeated, by my desire, by Dr. Physick now of Philadelphia, when he acted as House Surgeon* *at St. George's Hospital, whose accuracy I could depend upon*" [82]. He is notable of the many of Hunter's famous students as the one that Hunter offered to stay as his partner. Physick wanted to complete his education in Edinburgh at was there by May in 1791. He received his doctorate there the following year with his thesis on *Apoplexy* which was dedicated to Hunter [83]. He returned to Philadelphia in September of 1792 at the age of 24 and became the most well known surgeon of his era. In 1794 Physick was elected to the staff of Pennsylvania Hospital and to the Dispensary. His two favorite operations were cataracts and bladder stones where he used Cheselden's method learned from Hunter [84]. The aging John Marshall was the fourth Chief Justice of the United States when he presented to Dr. Physick at age 76 in 1831. On November 19th he performed a perineal lithotomy on Marshall and removed about 1,000 bladder stones (some are still on display at the Mütter Museum of the Philadelphia Medical Society. Marshall showed his appreciation to Physick by having a silver wine cooler inscribed to his surgeon which is still at the Old Pennsylvania Hospital Historic Collections, "*The tribute of gratitude for restored health offered by J Marshall. Philadelphia, November 19th 1831*" [83]. Physick's health began to decline; he had suffered from Yellow Fever and Typhus. Sadly, he too began to develop kidney stones and suffered from recurrent bouts of renal colic. He died on December 15, 1837 of congestive heart failure [81].

Another American surgeon, Ephraim McDowell (1771–1830) also trekked to England to advance his surgical skills and sent a copy of one of his first papers in 1817 to Physick on *Ovariotomy*. It was reported that Physick dismissed the paper because it was crudely written and an incomplete description, despite the remarkable fact that it was the first major transperitoneal operation reported. McDowell also had learned lithotomy, probably not the lateral approach from John Bell during the 2 years McDowell spent in Edinburgh (1972–1974) [85]. Two years following his first ovariotomy on Jane Todd Crawford (related to Mary Todd Lincoln), McDowell performed a successful perineal lithotomy on a 17 year old youth named James Knox Polk, later the 13th President of the United States [86]. The surgery was a success but Polk developed infertility following the surgical procedure and he and his wife Sarah were never able to have children [87].

We have already discussed Benjamin Winslow Dudley (1785–1870) who also pioneered surgical lithotomy in the United States in Lexington, Kentucky. He learned lithotomy with many of the greats of the 19th century, Abernathcy, Bayer, Cline, Sir Astley Cooper, Dupuytren and Dominique Larrey [88]. His results were as good as anyone's, and better than most (225 lithotomies with only 5 deaths) [89]. He further trained James Mills Bush who in turn remained at the Medical College of Transylvania as professor of anatomy and surgery. He also began to perform lithotrity following a trip to London and Paris and used both Heurteloup's and Jacobson's instruments in Lexington [78].

Henry Fraser Campbell (1824–1891) was one of the Southern surgeons who is somewhat obscure. He was born on February 10, 1824 in Savannah, Georgia. Campbell's father died early and the family moved to Augusta where he was influenced by two maternal uncles, Professor Joseph A. Eve, M.D. and Edward A. Eve, M.D. and a cousin Professor Paul Fitzsimmons Eve, M.D. who brought him into the medical profession. Henry graduated from the Medical College of Georgia at age 18 and was asked to join the faculty [90]. He was a prolific writer about a wide range of medical subjects, such as infectious diseases, neurology, general medicine, general surgery, obstetrics and gynecology, orthopedics, trauma, public health and preventative medicine, but his 1879 treatise Urinary Calculus is of interest to us here [91]. In this paper he summarizes the removal of bladder stones in 39 cases by the bilateral method of Dupuytren. He quotes all of the recent relevant literature, including the works by Coulson summarizing statistics on lithotomy (Table 18.4). In addition, he was fully aware of the critical anatomy of the region and the risk of fatal hemorrhage from the internal pudendal arteries, which he avoided. He had hemorrhage from the bulbar urethra but managed these with

Table 18.4 Coulson's 1853 tabulation of the outcomes from all lithotomies

Operation (method)	Number	%	Mortality	%
Lateral lithotomy	2,242	47	303	14
Apparatus minor	1,986	41	406	20
Suprapubic lithotomy	268	5.6	87	32
Lithotomy via rectum	85	3.9	38	21
Transversal lithotomy	112	2.3	23	21

packings of "*the tampon en chemise packed with pledgets of cotton-wool well saturated with a solution of Monsel's salt*" [91]. Twenty-one of his cases were in children, several were colored boys and there were no fatalities. He then reviewed the results in 20 adult male cases with bladder stones. Here there were 2 deaths, 1 in a 75 year old male who was in poor health and the other in a 35 year old who probably had urinary infection. They had only one significant post-operative bleed on the tenth post operative day, and Campbells's assistants emergently opened the wound and packed the bulbar urethra and stopped the bleeding. The patient survived making his lithotomy mortality an admirable 7 % [91]. He was commissioned as a surgeon in the Confederate States Army in 1861 and became medical director of the Georgia Military Hospital in Richmond. Before the war he was the Vice President of the American Medical Association and after the Civil War he became the president of the AMA in 1884. He died on December 15, 1891 [90].

Conclusions

> "*In lithotomy great awkwardness, mortifying failures and dangerous blunders are perhaps more frequently observed than in any other great operation in surgery. Many a surgeon, who contrives to cut off limbs, extirpate large tumors, and even tie aneurismal arteries, with éclat, cannot get through the business of taking a stone out of the bladder in a decent, much less a masterly style.*" [92]
>
> —Samuel Cooper, 1817

We began this chapter with the iconic history of the Caduceus now it is time to conclude with the Ouroboros (or Uroboros) which is another ancient emblem of the serpent or sometimes a dragon consuming its own tail. This symbolically represents the cyclicality or the constant re-creation of nature. Life itself is a cycle [93]. The first known use of this figure is in the Egyptian book of the Netherworld. The myth of the phoenix represents another incarnation of these beliefs that death is not an end, but a beginning or a part of a whole cycle in a cosmos where man has increasingly become relegated to an afterthought. Plato immortalized the self-eating snake in Timaeus. "*The living being had no need of eyes when there was nothing remaining outside him to be seen; nor of ears when there was nothing to be heard; and there was no surrounding atmosphere to be breathed; nor would there have been any use of organs by the help of which he might receive his food or get rid of what he had already digested, since there was nothing which went from him or came into him: for there was nothing beside him. Of design he was created thus, his own waste providing his own food, and all that he did or suffered taking place in and by himself*" [94]. The message of hope, that is implied by this last icon is that we can learn from our mistakes, grow as a profession, that past injustices and indignities need not be repeated, that the future is bright with possibilities, and man's pathway might be ascendant not descendant. For as the philosopher George Santayana stated, "*Those who cannot remember the past are condemned to repeat it*" [95]. As stones have afflicted human beings since before recorded history it is fitting to recall the ouroboros and circling back through the eras of mankind's desperation and the call for the lithotomist.

We will meet in some detail in the next chapter, a gifted and tenacious surgeon of the early nineteenth century who would nearly single-handedly develop a revolution in stone treatment, Jean Civiale. He was well known as the surgeon who developed lithotrity that his contributions to lithotomy are nearly completely overshadowed. Civiale's mentor during his early career was Dupuytren, a famous Parisian surgeon in his own right in 1816 not being content with the lateral operation created a two-bladed lithotome for a bilateral approach to the bladder. In 1825 and 1830 the median operation was re-popularized by Mr. Allarton in London often referred to as the Marian revival. Civiale also cut for stones when indicated. He combined the advantages of the median and the bilateral operation of Dupuytren which in turn became the standard method that his pupil, Mr. Henry Thompson would take with him back to London. Nélaton was the proponent of the pre-rectal operation which is only a carefully dissected bilateral procedure of Dupuytren. The Ouroboros metaphor applies when we observe Mr. Thompson's quote, "*When the problem is best solved, we shall have the best form of lithotomy. It is quite open to discussion whether we have yet found the best way, although we have been 2,500 years- to say nothing of the pre-historic period- in coming to our present position*" [96].

It is fitting to end with one final account of William Cheselden (Fig. 18.4c). He was a member of the Royal Society and must have known Sir Isaac Newton who was President for much of this time. On March 4, 1727 when Cheselden was at the peak of his prowess with the new lateral perineal operation, he was called to see Newton with his fiend Dr. Mead. They both went and examined the ailing Newton and both agreed that he was so ill that the surgical intervention had no hope helping and Newton passed away on March 20th [59]. Cheselden's friend and neighbor, Jonathan Richardson painted the famous portrait of Cheselden which is in the National Portrait Gallery and wrote these lines to Pope: [97]

Cheselden, with candid wile,
Detains his guest; the ready Lares smile;
Good Chiron so, within his welcome bower
Received of verse the mild and sacred power.
With anxious skill supplied the best relief
And healed with balm and sweet discourse his grief.

But Pope went one better in his *Imitation of Horace* [97]:

Weak though I am of limb and short of sight
Far from a lynx and not a giant quite
I'll do what Mead and Cheselden advise
To keep these limbs and to preserve these eyes.

"*A little learning is a dangerous thing;*
Drink deep, or taste not the Pierian Spring." [97]

—Pope

Addendum Lithotomies

Lithotomia Celsiana [18]

"*A strong, well-trained man sits on a high stool and seizes the boy- who is lying on his back- from behind, after having set the boy's buttocks on his knees. When the boy's legs have been drawn up, the man orders him to put his hands behind his knees, and to pull upon them as much as he can, and he too keeps them in this position. But if the body of the patient is stronger, two strong men sit on two stools side by side and the adjacent legs of the stools and the men's legs are lashed together, so that they cannot be separated. Then the patient is laid in the same way as described above upon the knees of the two men; and according to their position, one takes hold of the patient's left leg and the other grasps the right while at the same time the patient himself pulls upon his own calves. Whether one or two men hold the patient, they press downwards with their chests upon the patient's shoulders. Hence it results that the hollow between the iliac region above the pubes is stretched out without any folds, and as the bladder has been crammed into a narrow space, the stone can easily be seized. In addition, moreover, two strong men should be stationed at either side to prevent the one or the two men who are holding the boy from slipping. Then the two fingers, the forefinger and the middle, first one and then the other, into the anus of the patient and places the fingers of his right hand upon the hypogastrium, but lightly, in order to avoid injuring the bladder with the fingers should they apply violent pressure on the calculus from both sides. And, as holds in most cases, the procedure must not be carried out in haste, but in such a way that everything comes off as safely as possible, for an injury to the bladder causes spasm with a consequent danger of death. And the stone is first sought for about the neck of the bladder and when found there it is expelled with less trouble. And this is why I said that the patient must not even be treated except when the stone has been recognized by its special signs. But if it is not at the neck of the bladder, or it has slipped* *backwards, the fingers are placed at the base of the bladder and the physician must also move his right hand upwards and gradually follow the fingers downwards. When the stone has been found, and it must fall between the hands, it is guided downwards- and the smaller and smoother it is, the greater care that must be taken lest it escape, because we must beware of disturbing the bladder too often. There the physician's right hand is always kept above the stone, while the fingers of the left press it downwards until it reaches the neck of the bladder, towards which the stone must be pressed so that, if oblong, it will come out end on; if flat, it will lie crossways; if cubical, it will rest on two of its angles; if any part is larger, the smaller part will come out first. In the case of a spherical stone, it is clear that the shape makes no difference, except that if any part is smoother, this should be the first to be extracted. When the stone has reached this position, then the skin over the neck of the bladder next to the anus must be incised to the neck of the bladder by a semilunar cut, the horns of which point towards the hips; then a little lower down in that part where the incision is concave a second cut must be made under the skin, perpendicular to the first, to open up the neck of the bladder until the urinary passage is opened so that the incision is a little larger than the stone. For those who make a small opening for fear of a fistula, which in this place the Greeks call a rhyás, risk the same danger, but to a greater degree, because the stone, when pressed out violently, will make a way out by itself if it is not given one. And this is even more harmful if the shape or the roughness of the stone has led to any further trouble. As a consequence, haemorrhage and spasm may ensue. And even if the patient survives, he is nevertheless doomed to have a much wider fistula- if the neck of the bladder has been torn- than he would have had if it had been incised. Now when the neck of the bladder has been opened, the stone comes into view, and its colour make no difference. If it is small, it can be pushed outwards by the fingers on one side, and extracted by those on the other. If it is large, the hook made for this purpose must be put over the upper part of it. This instrument is thin at the end and beaten out into the semicircular shape, which smooth on the outer side (with which it comes into contact with the body), and rough on the inner side (with which it contacts the stone). And it must be rather long for a short instrument would not be strong enough to extract the stone. When the hook has been inserted, it must be inclined to each side to see whether the stone has been grasped, because if it has been firmly seized it moves together with the hook. This necessary lest- when the physician begins to draw the hook forward- the stone should slip inwards and the hook fall upon the lips of the wound and lacerate them. And I have already noted above how dangerous this is. When it is certain that the stone is firmly held, almost simultaneously a triple movement must be made: first towards each side, then outwards, but in such a way that the movement is gentle and the stone is at first drawn a little outwards; that having been done, one end of the hook must be raised so that it remains further in and the stone can be drawn out with greater ease. But if at any time the stone cannot be easily seized from above, it will have to grasped from one side. This is the simplest operation. But the various contingencies require some further observations. Indeed there are some stones, which are not merely rough, but also spiny, and these may be extracted without any danger if they have reached the neck of the bladder on their own accord. But if they remain inside the bladder, it is not safe either to search for them or draw them out, because if they wound the bladder they will cause a speedy death from spasm. This is all the more true should any spiny stone stick to the bladder, and, on being drawn out, have folded it over. That the stone is at the neck of the bladder may be inferred from the fact that the passing of bloody water in drops. In the presence of these signs we must test the nature of the stone with the fingers too, and the operation should not begin until we are sure of this. And then too, the fingers must be applied to the stone gently, lest they wound by moving the stone forcibly. The incision is made. Many use a scalpel here too, but since this is a rather week instrument, and may meet some prominence of the stone and after having cut the flesh over this prominence fail to cut what is in the hollow* *beneath, leaving something that necessitates a second incision, Meges devised and made a straight instrument, with a wide border on its upper part, semicucular and sharp below. Grasping this instrument with the two fingers, the forefinger and the middle, and putting the thumb upon the back of it, he pressed it down so that he cut both the flesh and any prominence of the stone at the same time. By this means he succeeded in making a sufficiently large opening with only one incision. But whatever way the neck of the bladder is laid open, any rough stone must be extracted gently and no force is to be used out for haste*."

Paul of Aegina [18]

"*I have already explained not only the cause of the formation of calculi, but also why they form chiefly in the bladder of boys, and in the kidneys in adults. Now I will speak about the method by which they can be extracted, after having described the signs of bladder stones. The urine is watery and has sandy deposits; the penis is tormented by a continuous pruritis, relaxes and grows erect again without any reason; the patients are irritated and rub it frequently, most of all the boys, and the flow of urine is suddenly blocked when a calculus sticks in the neck of the bladder. Boys up to fourteen years can safely be operated on, because they recover more easily owing to their tender bodies; old people are unlikely to recover, because wounds in their tough bodies heal only with great difficulty, but middle-aged people are a middle way have an average chance of recovery. Moreover, those who suffer from big stones recover more easily, because they are accustomed to suffering from inflammations, while those who suffer from small calculi recover with difficulty for the opposite reason. This being the case, when we have decided to perform the operation, first of all we must shake the patient, who will either be shaken from our assistant, or he himself shall jump down from a higher place, in order to push the stone to the neck of the bladder. Then the patient must be placed on a bench, on which he must sit erect with his hands under his thighs, to compress the bladder into a space as narrow as possible. That having been done, we must palpate the stone. Should palpation reveal that the stone, moved by shaking, lies in the middle region between the anus and the scrotum, we shall perform the incision. If, instead, this is not the case, we must grease the forefinger of our left hand with oil, if the patient is a boy, and also the middle finger, if the patient is an older man, and insert them into the anus, and then, searching for the stone with the finger tips and inching it along little by little once it has been found, we must block it in the neck of the bladder, push it outside, hold it firmly, and order one of the assistants to press the bladder with his hands and the other to pull the testicles upwards with his right hand while using his left hand to stretch the middle region between the scrotum and the anus towards the part opposite to the place where we shall make the incision. That having been done, we must take the lithotome and perform an oblique incision between the anus and the testicles, not in the exact midline between the scrotum and the anus, but laterally, near the left buttock, using the stone as a chopping-board. The incision must be wide enough at the surface, but small enough inside, as to let the stone come out easily. Sometimes the stone comes out immediately through the incision, if gently pushed by the finger or the fingers we have inserted into the anus, without the aid of any instrument. If it does not, we must extract it with the special hook known as the 'lithoulkós.' The stone having been extracted, we must stanch the flow of blood with styptic medicaments like manna, incense, aloe, comfrey, or also yew and the like and put wool or flax compresses soaked in wine and oil on the wound. Then we will bandage it with the six-tailed binding that is peculiar to lithotomy*."

Susruta's Lithotomy [24]

A person of strong physique and unagitated in mind should then be made to sit on a table as high as the knee-joint. The patient should be made to lie on his back on the table, placing the *upper part of his body on the attendant's lap with his waist resting on an elevated cushion. His elbows and knees should be flexed and bound up with fastening of linen (sataka). After that, the umbilical region of the patient should be well rubbed with oil or clarified butter and the left side of the umbilical region should be pressed down with a closed fist so that the stone comes within reach of the operator. The surgeon should then introduce into the rectum the second and third fingers of his left hand duly anointed and with the nails well pared. The fingers should be carried upwards toward the raphe of the perineum so as to bring the stone between the rectum and penis where it should be so firmly pressed as to look like an elvated tumor.*

An incision should then be made on the left side of the raphe of the perineum and of sufficient width to allow the free egress of the stone. Speical care should be taken in extracting the stone so that it will not break into pieces or leave any broken particle behind, however small, as they would in such case be sure to grow large again. Hence, the entire stone should be extracted with the help of an Agrabakra yantra (an instrument with a long handle and flattened end bent in the form of a wide scoop.

William Cheseldon (via John Douglas)

"*Every thing necessary being in this manner got ready, the Patient, in a loose Night-Gown, his Head and legs covered, but nothing tight about his Neck or Belly, is brought from the Cutting-Ward in the Hospital to the Theatre, for here I suppose the scene of Action, and laid on the Table, his Head resting on the Pillow, and his Hips on its lower Edge. In this situation he is tyed, as in the greater Apparatus. that is, his Wrists are gently brought down to the Out-sides of his Ancles, and secured there by proper Bandages, his Knees having first been bent, and his Heels brought back near his Buttocks: then, his Thighs being raised and separated from one another, he is kept in this Posture by two Assistants (commonly Apprentices to some of the Hospital Surgeons) during the whole Time of the Operation, they holding his Ancles with one hand, and his knees with the other: there is one more standing at his Shoulders, in order to prevent his rising up or retiring from the Operator while he makes the incision.*

Then, Mr. Cheselden, standing before the Patient at the End of the Table, takes the Catheter, first dipt in Oil, and introduces it in the usual Manner through the Urehtra into the Bladder, where having searched for and discovered the Stone, he delivers it to one of his fellow Surgeons standing on his Right-hand, whom he desires first of all to satisfy himself whether there be a Stone or not; and then his Assistant, holding the Handle between the Fingers convex Side close up to the Os Pubis, near the Commissure of Joining of the Bones, to remove or bear up the Urethra as far as may be from the intestinum Rectum, being frequently desired by Mr. Cheselden, not to push it down, nor make the convex or grooved Side thrust the Parts forwards or outwards towards the Perinaeum; for tho' by so doing the Place of the external Wound would in some measure be ascertained, and the Groove of the Catheter be more easily found in making the internal one; yet the Danger of bringing the Urethra nearer the Rectum, which, in that case, is more liable to be cut, does more than counter-ballance these seeming Advantages. Besides, in his Method of operating, there can be little Occasion for any such Contrivance, were it attempted with no Inconveniency, the external Wound being very large and deep.

The Staff being fixed in this Situation, and its grooved Part being turned outward and laterally, Mr. Cheselden sits down in a low Chair, and drawing the Patient nearer him, till his Buttocks reach a little over the End of the Table, his Feet being quite off from it, takes his Knife, which he sometimes arms with a little Tow rolled about it, to prevent his Fingers from slipping when it becomes wetted with the Blood, and holding it firm in his Right-hand, his Thumb on the Inside of the Blade, his Fore-finger on the Outside opposite to it, his Middle-finger on the Outside of the Handle, and the Extremities of the rest on its upper Edge. Then distending and keeping steady the Skin of the Perinaeum with the Thumb and

Fore-finger of the Left-hand, he makes the first or outward Incision, through the Integuments from above downwards, beginning on the Left-side of the Raphe or Seam between the Scrotum and the Verge of the Anus, almost as high up as where the Skin of the Perinaeum begins to dilate and form the Bag that contains the Testicles; and from thence he continues the Wound obliquely outwards, as low down as the Middle of the Margin of the Anus, at about half an Inch distance from it near the Skin, and consequently beyond the great Protuberance of the Ischium. The first or upper Part of this Incision is but superficial; after that he plunges his Knife much deeper by the Side of the Rectum, and finishes it by drawing his Knife obliquely towards himself; these three Motions may always be observed in his external Incision, but the last is performed pretty much at Random, there being her no Danger of doing any Mischief; and indeed I have, however, often observed that he is very little sollicitious about the precise Place and Limits of the external Wound, for I have seen him sometimes cut the Skin much nearer the Anus; sometimes at a greater Distance from it; sometimes he begins the Incision very high up, at other times lower down (and all this Variety in Patients of the same Bigness or Size); but his Intention and principal Design is to make the Wound as large as he can with Safety, always avoiding to wound the vesicular Membrane of the Scrotum.

Having cut the Fat pretty deep, especially near the Intestinum Rectum, covered by the Sphincter and Levator Ani, he puts the Forefinger of his Left-hand into the Wound, and keeps it there till the internal Incision is quite finished; first to direct the Point of his Knife into the Groove of his Staff, which he now feels with the End of his Finger, and likewise to hold down the Intestinum Rectum, by the Side of which his Knife is to pass, and to prevent its being wounded. This inward Incision is made with more Caution and more Leisure than the former.

His Knife first enters the Groove of the rostrated or strait Part of his Catheter, thro' the sides of the Bladder, immediately above the Prostate, and afterwards the Point of it continuing to run in the same Groove in a Direction downwards and forwards, or towards himself, he divides that Part of the Sphincter of the Bladder that lies upon that Gland, and then he cuts the Outside of one half of it obliquely, according to the Direction and whole Length of the Urethra that runs within it, and finishes his internal Incision, by dividing the muscular portion of the Urethra on the convex Part of his Staff.

When he first began to practice this Method, he cut the very same Parts the contrary way; this is, his Knife enter'd first the muscular Part of the Urethra, which he divided laterally from the pendulous Part of its Bulb to the Apex, or first Point of the prostate Gland, and from thence directed his Knife upward and backward all the way into the Bladder; as we may read in the Appendix he lately published to the Fourth Edition of his Book of Anatomy. But some time after he observed, that in that Manner of Cutting, the Bulb of the Urethra lay too much in the way; the Groove of the Staff was not so easily found, and the Intestinum Rectum was in more Danger of being wounded.

A sufficient Opening being made, Mr. Cheselden rises from his Chair, his Finger still remaining in the Wound, and calling for the Gorgeret, he puts its Beek into the Groove of the Catheter, and so thrusts it into the Cavity of the Bladder, where he is often at once sensible of the Stone, which thus becomes a Direction to him when he uses his Forceps.

This done, he draws out the Staff, and holding the Gorgeret in his Left-hand, he introduced the Forceps, the flat Side uppermost, sliding them with great Caution along its concave Part, nicely observing when they pass the Wound into the wide Part of the Bladder and then he withdraws the Gorgeret, and taking hold of the two Branches of the Forecpes with both his Hands, he searches gently for the Stone they being still shut, and having felt it, he opens them, and endeavours to get the uppermost Blade under the Stone, that it may fall more conveniently into their Chops, and so be laid hold of; which being done, he extracts it with both Hands, one upon the Ends of the Forceps, the other about the Middle, but with a very slow Motion to give the Parts time to stretch and dilate, which he promotes by turning the Forceps gently in all Directions, taking all possible Care that it *may not slip; of which if he perceives any Danger, he endeavors to recover it again without pulling his Forceps.*

If the Stone is pretty large and smooth, and lies in that Sinus of the Bladder on the same side with the Wound, he draws it out with the greatest Facility imaginable, in Subjects of all Ages. But when he observes that the Stone is either very small, or does not lie right to the Forceps, he immediately pull them out, and introducing his Finger into the Bladder, he tries to turn it, and to disengage it from the Folds of the inner Membrane, in which it is sometimes entangled. Then he thrusts in his Gorgeret upon the upper side of his Finger; which being drawn out, he turns the Gorgeret, and introduces his forceps, and so extracts the Stone; but without any manner of Hurry or Precipitation…

He performs this Operation with so much Dexterity and Quickness that he seldom exceeds half a Minute, unless when he is obliged to take up and tie the Vessels before the Stone is extracted, or when there happens to be something uncommon in the Stone itself."

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Lithotrity and Litholapaxy

19

Introduction

> "*The surgery of stone till about fifty years ago was simply the surgery of stone in the lower urinary tract. Calculi impacted above the bladder were considered quite beyond the reach of operative treatment*." [1]
>
> —J. Swift Joly (1929)

We have just finished the historical discussion of lithotomy, "*cutting for the stone*," and now we are turning to another surgical technique. Why does a now relatively esoteric method that lasted less than 100 years deserve any special attention? The simple reason lies behind all the future of surgery itself. The less invasive a surgical intervention, largely holding all variables the same, then the better the outcomes for the patients. Now this type of statement is tantamount to heresy amongst some surgeons; however, given keeping skill sets the same (or the ability to dexterously perform a given task), this rule applies to most types of surgery, and we will get to this point in the last chapter called Six Sigma. Or perhaps as Harry Houdini is thought to have suggested "*the magic is in the magician, not the magic wand*."

Next it is advisable to again discuss terms utilized throughout this chapter. It is noted that the surgeons who are often developing the techniques we are going to discuss may well have used a different term, for instance, Civiale, whose work we are going to scrutinize, used the term lithotripsy for much of his work. Using modern classification semantics, the correct term was lithotrity—mechanically breaking the stone or stones. Litholapaxy simply means to break the stone and evacuate the fragments. Lithotripsy is now the term used to destroy a concretion using some powered device. For our historical consideration, therefore, we will in this chapter concern ourselves with the first two and put off lithotripsy for consideration in a later chapter.

We have already mentioned that the concept of lithotrity was not a new concept when it came to Civiale. Ammonius of Alexandria (third century, about 230 BCE) was a surgeon and lithotomist who had been reported to have improved upon the methods for breaking stones for easier extraction. Apparently after opening the bladder, he would trap a larger stone with a hook and then split or shatter the concretion with a thin blunt instrument. He earned the nickname "*lithotomus*" [2]. Sadly, there are no surviving primary references from him or his time in Alexandria, only the aforementioned reference to him by Hippocrates. The Sushruta Samhita an ancient Sanskrit writing also mentions lithotrity and describes a screw-based metal stone-crushing forceps [3]. Experienced lithotomists almost always had some type of instrument in their instruments that could crush a larger stone into fragments for an easier extraction. Albucasis (1090) describes a lithotrity by perforating and breaking up urethral calculi. He recommends that the penis be tied between the calculus and

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the bladder to prevent the stone from being pushed backwards. This done, he directs the stone to be perforated with a kind of bore (terebra) [4].

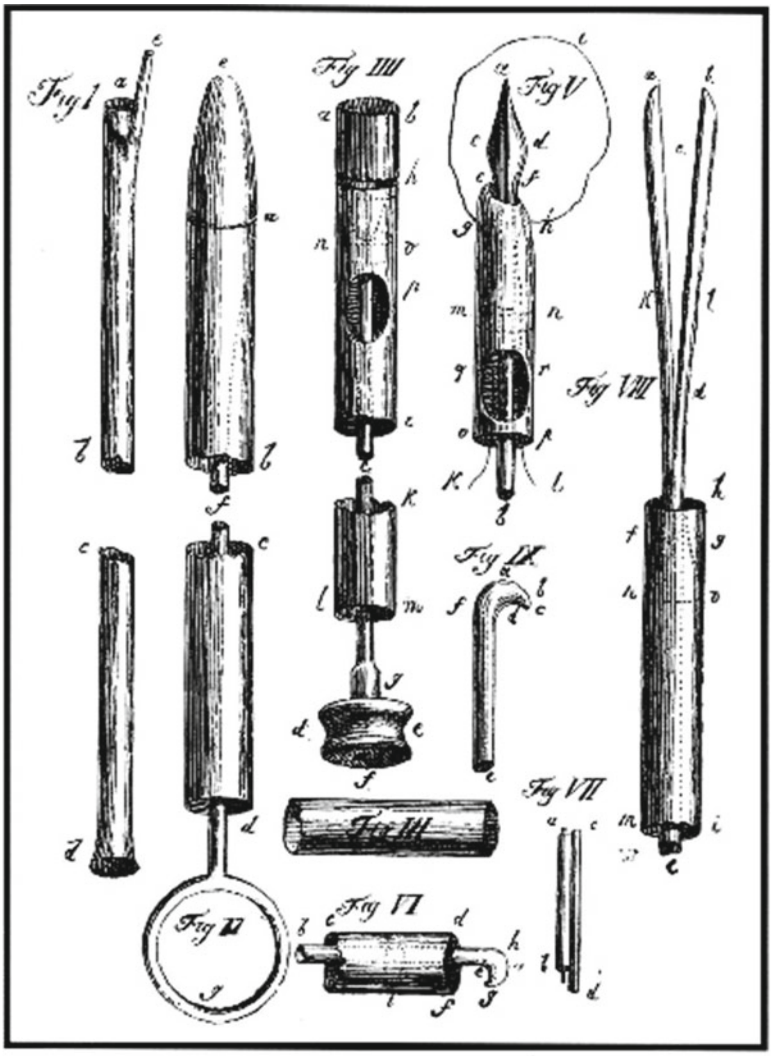
Early Attempts at Avoiding Lithotomy

Pierre Franco in 1561 repeated this advice of Albucasis describing and drawing an instrument for perforating the stone which he probably borrowed from Guido de Caulic (1546) [5]. Franco also used an instrument he calls *vesical á quatre*, for extracting calculi from the bladder. This was an iron rod supporting four branches at its extremity and enclosed in a cannula; when pushed forward the branches opened sufficiently to grasp a stone as large as an egg [6]. Guilhelmus Fabricius Hildanus (1560–1634) reduced the four-bladed device down to three blades [7]. We have already described the Reverend Stephen Hales (1677–1761) in our chapter on Enlightened Minds. Hales had an amazing quality of grasping complex problems and thinking them through and, even with little information or experience, would intuit solutions that eventually would become accepted. Not only did he develop a double-lumen catheter, he also devised an ingenious forceps device that could extract urethral stones that would eventually get rediscovered by the likes of John Hunter: "*I cut off the lower end of a straight Catheter for a Stillet or Forceps to pass thro'; the lower end of the Forceps was divided into two Springs like Tweezers who Ends were turned a little inwards*" [8]. Sir Astley Cooper continued the tradition of developing innovative instruments to aid in the extraction of stones, crush smaller bladder stones, and extract fragments [9].

Alfonso Ferri (1553) described an instrument that contained an external cannula, the three-bladed forceps, and a working screw to tighten the blades [10]. Hildanus further modified the mechanism incorporating a fly screw [7]. Loiseau described a lithotrity of a urethral stone of a monk in the sixteenth century. Also in 1506, Antonio Benivieni performed a percussion lithotrity (way before Baron Heurteloup) [10]. He explains that he used a hook behind the calculus in order to "fix it" and struck it repeatedly with an iron rod: "*Uncum calculo injecio ne silicit concussus iterum in vesicam revolveretur. Tum feranuento priore paste retruso, calculum ipsum percutio done, saepiu ictus in frustra comminuitur*" [11]. Marianus Sanctus lived in the early part of the seventeenth century and was noted by Haller, the famous physician who read and commented on his lithotomy technique to have devised an instrument for extracting bladder calculi and fragments. Ciucci in 1671 speaks of a "*tenacula tricuspis*" as the most effective method of curing stone by grasping and breaking it into fragments [11]. Thomassini in 1791 also described breaking smaller, friable bladder stones with instruments [11]. Rodriguez in Malaga, Spain, also mention lithotrity in 1800 [11].

By the dawn of the eighteenth century, the significant mortality and morbidity of the perineal lithotomy surgery was beginning to have gifted surgically minded physicians beginning to seek other methods to destroy stones (almost 20 % mortality). The chemistry and the possibility of chemicals to aid the dissolution of stones made innovators look at hybrid methods of destroying bladder stones. General Martin of Lucknow claimed to have broken up a stone in his own bladder by means of a small curved metal sound with its end slightly roughened so as to file down the stone gradually over time in 1783 [12]. It supposedly took the general over 9 months to file down his concretion, but the instrument is in the collection of the Royal College of Surgeons museum. Franz von Paula Gruithuisen (1774–1852) was born on March 19, 1774, in a hunting lodge Haltenberg-on-Lech in upper Bavaria. Gruithuisen was apprenticed as a barber-surgeon during the war against the Turks, and he gained service and quickly became skilled as an assistant surgeon at the age of 14 [13]. Following the war he returned to his profession and began learning Latin, physics, astronomy, and languages. He gained a significant reputation for his skill and scholarship, and the Prince Elector Karl Theodor financed his education at the University of Landshut. He matriculated at age 27 and studied philosophy, natural sciences, and medicine. He received his doctorate in 1808.

He was a prolific author, scientist, as well as teacher at the School of Country Doctors in Munich. He published his paper *Should One*



Gruithuisen's instruments for lithotrity. 1813

Fig. 19.1 Franz von Paula Gruithuisen's 1813 illustrations of his transurethral lithotrity instrumentation. (*Fig. I*) Perfusion system. (*Fig. II*) Component of lithotrepan. (*Fig. III*) Length was 45 cm. (*Fig. IV*) Housing of lithotrepan. (*Fig. V*) Wire loop catches and holds stone. (*Fig. VI*) Hook for crushing stones. (*Fig. VII*) Galvanic spark device. (*Fig. VIII*) Two-armed crushing forceps

Abandon the Long-standing Hope of Being Able to Remove Bladder Calculi Mechanically or Chemically Sometime in the Future? in the 1813 Journal of Medicine and Surgery [13]. He had experimented on animals, corpses, and occasionally on himself prior to publishing his work. He included an illustration of the instruments in this treatise (Fig. 19.1). He also discussed the six options for treatment at the time: lithotomy, aqueous perfusion, chemical dissolution, galvanic shattering, mechanical shattering, and the combination of any of these. He believed that a combination approach had the greatest chance for success. His instruments demonstrate this combination approach. Figure I is a perfusion system with the solution delivered through "e" and effluent out via "a." Figures II, III, and IV are components of the lithotrepan which was 45 cm in length. There were serrated sawlike devices and a sharp pointed drill. Figure VI is a stone punch, and Figure VIII is a two-armed crushing forceps. Figure VII is a galvanic, electrical spark device for trying to explode calculi. Figure V shows the wire loop that would trap and hold the calculus which could be bored, drilled, punched, or blasted. All pieces could also then be chemically treated for further dissolution. All in all, quite ingenious and he utilized straight instruments which is what he spent the most time on cadavers studying. The idea of drilling holes into the calculi was thought to improve the chance for dissolution by increasing the surface area or the irrigation solution. Also bits of stones would be flushed out giving him a chance to analyze these and alter his fluid solutions. His lubricant was the albumin from chicken eggs. One final note is that Gruithuisen predicted his own anonymity with his concluding remarks in his paper, "*One proceeds progressively to art from the idea of art; one comes to science from experience. It is of no consequence who was the first to have had the idea for the artifice; the accolade and merit belongs to whoever puts it into practice*."

Others were also beginning to investigate the ability of instruments to crush stones, especially smaller bladder stones. Elderton from Scotland tried a curved stone-crushing instrument in 1819 [11]. Sir Astley Cooper had his instrument maker John Weiss devise a crushing transurethral forceps, and he removed 84 calculi in seven sessions from the Rev. Mr. Bullen of Barnwell, Combs, in 1822 [14]. Isaiah Lukens of Philadelphia also devised a forceps with a watch spring basket and drill for bladder stone destruction in 1825 [15]. It would appear that everyone everywhere was preparing for great changes in the management of this ancient affliction.

Civiale

Jean Civiale was a precocious second year medical student at the University of Paris and attended the lectures of Jean Nicolaus Marjolin (1770–1850) who was interested in the problems of bladder stones. He then began contemplating destruction of bladder stones and to invent innovative devices to try and capture stones. He certainly did know of the methods of Franz von Paula Gruithuisen (1774–1852) [16]. Civiale does mention the work of Gruithuisen briefly in his textbook, "*In 1813, the Bavarian Dr. Gruithuisen stated in an article in the Salzburg Journal that catheterization was also performed with straight probes. He provided new evidence that this operation was easy to carry out. Since 1817, I have used such instruments almost constantly in my practice*" [17]. He became an assistant of Dupuytren at age 28. He applied to the French Minister in July of 1818 for pecuniary aid toward constructing his instruments and wrote his first known written ideas entitled "*Some Details of a Lithotriptic*" that same year (Fig. 19.2) [11]. He included his drawings for three of these instruments in this treatise. The instrument consisted of two hollow metal tubes, gliding one on the other, the internal one supported at its distal end six steel branches (or graspers), slightly curved at the end but solidly fixed to the inner tube. In the original drawings these are shown as being joined to the tube by hinges, but this was an error of the artist for Civiale distinctly states that they opened by their elasticity with no allusion to any hinges. He called his working instrument "*the lithotriteur*" [11]. This consisted of a long steel rod, either lance shaped or dentated (he got this idea from Gruithuisen's) originally needing substantial twisting by the fingers alone but with practical experience on cadavers he would soon correct this short coming. The Minister of the Interior sent the application on to the faculty of Medicine, and Percy and Chaussier reported upon the student's invention—but they probably took no notice of it. In 1819, the branches were reduced from six to four, and by 1820 he further reduced the number to three. In 1820 he added his bow drill to rapidly increase the ability to drill through stones. With the improvements now made, he made his first public experiments in 1822 at the Hôpital la Pitié in the morgue [11]. During this time, Mr. Elderton of Edinburgh published in April of 1819 in the Medical and Surgical Journal a proposal to crush bladder stones with a curved, two-branched instrument with a perforator (Fig. 19.2). By early 1822 Civiale was working on more cadavers with

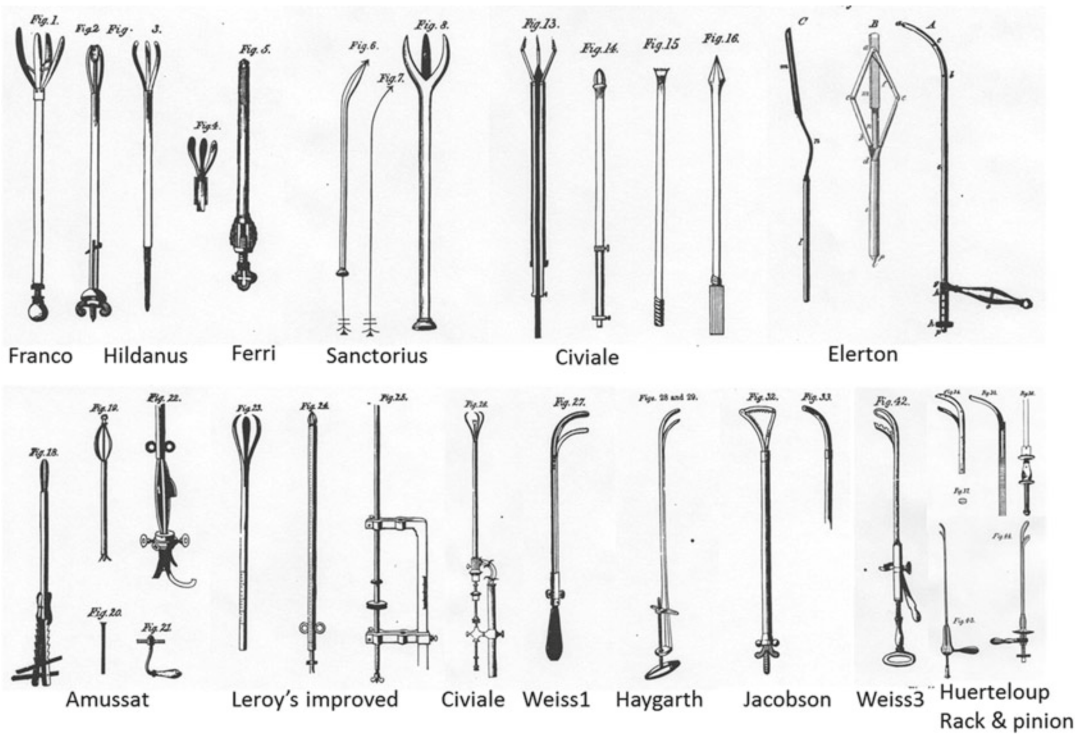


Fig. 19.2 Comparison of various instruments for crushing bladder stones for visual comparison to Table 19.1

implanted hard stones the size of hen's eggs and was successful in five out of six attempts. M. Amussat in April 1822 described a new instrument for stone crushing (Fig. 19.2). This was a strong-jawed, two-bladed forceps that could be extended from its housing cannula and crushed with the aid of a lever. This was followed by M. Leroy who began to be called Leroy d'Etiolles who also introduced an instrument in June of 1822. His device consisted of an outer silver sleeve and an inner extrudable basketing device that fixed the calculus and was spring loaded. There were several types of perforators which were turned by a bow drill [11].

With the upswing of interest now in bladder stone instruments, a commission was appointed by the Academy of Medicine in July of 1822 to examine all of these instruments. M. Amussat's broke, Leroy's worked better, but he went back to the drawing board. He would later return with new and improved device, like Alfonso Ferri's extractor (Fig. 19.2). The return of Leroy's new device forced Civiale to publish his work to date in May of 1823 entitled "*Retention of Urine, Urinary Calculi, and the possibility of destroying Calculi in the Bladder without Operation*" [11]. He also appended his original memoir of 1818 with the original drawings and demonstrated his mechanical improvements over the past 5 years (Fig. 19.2). Civiale failed however to describe in detail his improved surgical apparatus. In January of 1824 he addressed to the institute another memoir which was again referred to Percy and Chaussier, but this time they agreed to a demonstration which occurred on January 13, 1824. He performed his first lithotrity in the presence of the Commissioners (Larrey, Percy, Chaussier, Sedilot, and others), and the patient was freed from stones in two sittings. The second patient was operated on February 4, and the stone was removed in four sittings. On March 4 Civiale cured his third patient again with complete success but now attracting substantial attention. Envious rivals and those jealous of his skill rapidly

Table 19.1 Comparison of various instruments [Coulson, William: On Lithotrity and lithotomy. Lancet 1852;1(2):1–4]

Inventor	Name	Est. date	Place
Ammonius		200 BC	Alexandria
Sushruta		500	India
Albucasis	Lithotomos	1090	Persia
Antonio Benivieni		1506	Italy
Alexander Benedetti			Italy
Pierre Franco	Qudrupulus vesicae	1561	France
Marianus Sanctus		1636	Italy
Ciucci	Tenacula tricuspis	1671	Italy
Thomassini		1791	Italy
Fabricius Hildanus			Germany
Gruithuisen	Lithotrepan	1813	Germany
Civiale	Lithontripteur	1817	France
Elderton		1819	Scotland
Amussat	Crushing forceps	1822	France
Leroy	Lithoprione	1822	France
Civiale	Improved model	1823	France
Luken	Lithokonion	1825	Philadelphia
Haygarth		1825	
Weiss/ Cooper	Lithotrite	1830	England
Heurteloup	Percuteur courbe or Perce-Pierre	1831	France/ England
Key	Trigger percussor	1833	England
Fergusson/ Brodie	Rack and pinion screw	1835	England
Hodgson	Wheeled screw		

attacked his priority claims [16]. His first theory was close to that of Gruithuisen; he invented a trilabe grasping instrument that he could entrap stones and then drill into them. The legend has it that he would walk around with a stone in his pocket practicing his proficiency of finding the stone and capturing them all throughout the rest of his medical school career. His trilabe was a straight metal tube with an inner three-pronged grasping device [11]. He invented ingenious instruments that could be passed through the trilabe and bowed-string driver to rapidly drill into stones (Fig. 19.2).

Civiale had success after success and applied to and received a several bed ward at the Necker hospital. He contributed some of his own funds to continue his specialized unit that concentrated solely on urinary tract diseases. He had become world renowned for his technique and his instruments treating the wealth and royalty [18]. Henry Thompson from London came and he was taught lithotrity by the master. Civiale however did not have time or the inclination of the great teacher; he left no legacies with famous students, other than Henry Thompson. His legacy became the Necker Hôpital where Antonin Desormeaux (1815–1882) first brought his cystoscope in 1862, and he perhaps worked right next door to Civiale [18].

The French Group

Charles Louis Stanislas Heurteloup (1793–1864) was another bright young Parisian interested in lithotrity and became an outspoken proponent of lithotrity as well as a critic of Jean Civiale [19]. Heurteloup kept refining his instruments and used several names for them, one being called the "brisecoque" or shell breaker (Fig. 19.2). This consisted of a metal cannula with two rods ending in a strong claw attached to external springs and gears to apply force to break stones [11]. Baron Heurteloup was the first person to practice lithotrity in England. In 1829, he set up practice with the support of Anthony White, surgeon to Westminster Hospital. He described this "*percuteur courbe a marteau*" in 1832. With male and female blades, the stone was crushed by hitting it with a hammer. Heurteloup's instrument had multiple problems, and he presented it to the Westminster Society. It was originally made of three pieces so that when the blades closed on a calculus, the pressure produced by percussion caused a tilt at the slit of the male branch where it was riveted and acted as a lever that did little to improve upon the applied force to the stone [11]. Civiale's preceptor, Dupuytren, in fact wrote to Heurteloup "*If you could discover a mode of substituting for percussion a force of pressure which would enable us to do away with your bed, & c., I should at once advise the commission to award* *you the grand prize*." Baron Heurteloup's percussion instrument was called a "*percutor*," and he devised a special bed or table for treating bladder stone patients (Fig. 19.2) [19]. He invented a rectangular firm table where the patient was positioned in the lithotomy position. He had a rigid rod or what he called a "*fixed point*" which was firmly attached to the frame of the table so as to steady the percutor [19]. Heurteloup's percussor was the most popular crusher in these infant years of lithotrity.

Dr. Costello immediately recognized this flaw and corrected it in a two-piece instrument, which he in turn presented to the Westminster Society on December 8, 1832. He simplified Heurteloup's design and removed the teeth from the female jaw making the instrument remarkably close to the original design of Weiss [11]. Weiss was not done either; he took the modifications further and created a screw-torque instrument for Sir Benjamin Brodie (Fig. 19.2). This added power to break even the hardest calculi and fulfilling Dupuytren's request, but with a German/English method. Weiss demonstrated his screw mechanism also to the Westminster Society and showed that it acted with great crushing power even on hard calculi, so much so that the Society was frightened that the fragments might be injurious to the bladder wall [20]. The screw-type lithotrity instruments were rapidly supplanted by both English and French manufacturers of rack and pinion devices that were much more controlled in the application of the crushing force to the bladder stones.

Jean-Jacques-Joseph Leroy d'Etiolles (1798–1866) appears to have been on relatively good relationship with Jean Civiale initially: "*He seems to have been a better mechanic than Civiale but less interested in operating, for he did not perform his first lithotrity until several years after Civiale had started and then only after much persuasion by Heurteloup*" [20]. Leroy designed several instruments for grasping stones but settled upon a three- or four-clawed instrument like Civiale (Fig. 19.2). He also developed a bow-driven drill device for boring into stones. He called his instrument a *lithoprione* in 1825 [11]. The French appeared to have cornered the market on lithotrites by 1829 until a Danish surgeon named Ludwig Lewin Jacobson (1783–1843) designed a unique device in that year (Fig. 19.2). In 1833 the Académie des Sciences awarded Jacobson one of the Monthyon prizes (4,000 francs), having previously awarded him a gold medal for his important researches into the venal system of the kidneys in birds and reptiles. His lithotrite was unique; it consisted of a straight cannula and two curved, articulated three-hinged lasso-graspers. This was capable of generating great pressure on the entrapped stone using a winged-nut driver. Velpeau, the loquacious critic of Civiale, modified Jacobson's device by increasing its curvature of the blades and replaced the wing nut with a rack and pinion method that was far more efficient. Heurteloup was not finished though his percussor stimulated the London instrument maker Weiss to continue to develop innovative designs (Fig. 19.2). Weiss indeed modified his 1824 prototype to a much improved version by 1832. Heurteloup's, Weiss's, and Jacobson's devices had become much more popular than Civiale's, and the French instrument designer Charrierè modified Leroy's design with a spline-nut which greatly increased the power and efficiency of his lithotrite [21]. Charrierè would make Henry Thompson's lithotrite.

Vincenz Kern and Orthodoxy

Now Civiale's technique and much of what he was writing in regard to the surgical gold standard of the time, perineal lithotomy, were not universally accepted. We now can review some of the response to his threatened change of the status quo. Medical and lay readers of the time were enthralled by the rhetoric and discussion of the Academy Royal over the issue of what appeared to be a godsend of modernity, the breaking of bladder stones. One of the voices of discontent was M. Velpeau, a well-known lithotomist in Paris. It is worth our while to quote him at length in regard to the statistics presented in favor of lithotrity at the Academy Royal [22]:

> *Where consists the cruelty of drawing rigorous comparisons between lithotomy and lithotrity? Where lies the danger of lithotomy? In the wound.*

And what bad consequences may the inflicting of this wound give rise to? It may give rise: 1, to hemorrhage, which is rarely serious, 2, to a wound to the rectum, which is rare and of little importance; 3, to perforation of the bladder, still more rare; 4, to accidents affecting the nervous system, also very rare; 5, to cystitis, often mortal; 6, to peritonitis, phlebitis, or urinary infiltrations, which are not less formidable; 7, to fistulae, incontinence, impotence, which may be considered as simple infirmities, from which the patient most commonly recovers, lastly some fragments may remain in the bladder! Here is a chapter of accidents long enough, no doubt; but wait a moment, and you shall see that the lithotritist travels over a path covered with thorns. The dangers of lithotrity result from the necessity of keeping a large straight instrument in the urethra. It will be answered, perhaps, that the instrument now used is curved; but there is a great mistake on this point the curvature, being situated at the extremity of the instrument, renders its introduction more easy; but the portion that occupies the urethra is nevertheless straight; hence arises compression and violence to the prostate gland, the membranous urethra, and about the symphysis of the pubis; hence shocks to the nervous system, to such a degree as to prove fatal, contusions, lacerations, infiltrations; also abscess of the urethra, of the prostate gland, of the scrotum or perineum; hence sufferings so severe that, although inadvertently designed trifling by M. Amassat, they were aptly compared by one of his patients to the agony of extracting a tooth, the most frightful perhaps that can be borne. But this is not all; severe attacks of fever, dangerous inflammation of joints, urethritis, phlebitis, hemorrhage, perforation of bladder or rectum, fistulae, are also consequences of this instrumentation, without taking into account that cystitis, and inflammation of the ureters and kidneys are more common after lithotrity than after lithotomy. We may further add, retention of urine, peritonitis, instruments broken and which cannot be removed, the suffering and mischief caused by calculous fragments lodging in the urethra, and we shall then have an idea of the little danger attending lithotrity, that mild and gentle operation! The public are misled, because the accidents of lithotomy occur either immediately, or so soon after the operation, as not to be separated from it whilst those of lithotrity arise more gradually, even at a period so remote that both operator and patient believe them foreign to the treatment. Again, lithotomy either kills or cures; but lithotrity often does neither, at the same time that it lays the foundation for insidious mischief, which shows itself in disease so gradually that, without any breach of faith, it is assigned to some other cause. In short, this new operation, which is to a certain extent good, has hitherto been treated as a spoiled child, its advocates concealing all its defects, and setting forth, with too much ostentation, its good qualities; if we let this state of things go on, one abuse will follow another, until, under the support of this kind of nepotism the operation will be ruined, since it is admitted that nepotism answers no better in the end for a surgical operation, than for the success of an individual. The language employed in its favour threatens to throw this operation into the hands of the mechanics and adventurers; the means of rescue are, to remove it from the bosom of its parents and family, and to merge it in the circle of general surgery, where, being viewed by broad daylight, the evils which attend it will be separated from the good, and the operation will in due time be estimated at its just value." [22]

That is some historical rhetoric to be sure; no wonder both the lay and medical readers were so enraptured with this diatribe. There was no real data, other than Civiale's, and he for sure was using most of them to his advantage, as was noted by Velpeau [22]. We can also look at a more serious attack that was mounted from far away in Vienna, Austria, coming from a serious surgeon with really good data and better-than-average outcomes. Vincenz Kern was born in 1760 in Graz, Austria, and became a leading instructor in surgery during the late eighteenth and early nineteenth century. He was professor of surgery and obstetrics in Ljubljana in 1797 and became the professor of practical surgery at the University of Vienna in 1805. Kern founded a surgical reading society to give his students access to the scientific literature and fostered public discussion of completed case histories going so far as to challenge his students to criticize his own teachings. He had learned the lateral lithotomy from Pajola in Venice when he was visiting Vienna in 1803. Kern also went to visit Pajola in Venice to further sharpen his skills at perineal lithotomy. His first lithotomy was on a 7-year-old boy in 1803, and he published this report. Kern would go on to publish his series of bladder stones, honestly recounting even his failures. For instance, he reported upon a 34-year-old patient whose stone was so large that it had to be fragmented and extracted in 34 pieces which took him over 1 h! [22]. In 1808 he published his first 28 lithotomies all with good outcomes. Only later in his career did he bring together the wealth of his surgical experience as a comprehensive book Die Steinbeschwerden der Harnblase, ihre Verwandten Übel, und der Blasenschnitt, bei beiden Geschlechtern in 1829 [22]. This work was an overview of bladder stone disease, and he describes lithotomy, noting that he had performed 344 cases with only 31 deaths (an admirable 9 %) [22]. Kern washed his wounds with cold water believing this aided hemostasis; he washed his wounds with warm water postoperatively and used clean linen dressings (he had rediscovered the work of Henri de Mondeville). He also had modified Pajola's surgery (hence Le Cat's and also Frere Jacques) by incising the prostate from the top and sideways with a bulbous knife, then dilating the bladder neck. He believed that his modification had reduced the rate of postoperative fistulas which were rare in Vienna [22].

After Civiale published his work in 1824 but did not get widely distributed until 1826 [23]. Kern quickly wrote a paper in response to Civiale's claims in 1826 entitled *Bemerkungen über die neue, von Civiale un LeRoy verübte Methode, die Steine in der Harnblase zu zermalmen und auszuziehen* [24]. He begins "*How many times have we while performing our lithotomies experienced the unending bitter burden to remove each single fragment when the stone due to its low cohesive ability fragmented during the extraction; and beyond this, had to tolerate the hostile and unreasonable accusation: fragmentation of the stone is always proof of the lack of dexterity of the operating surgeon. How curious! What usually is made an accusation for the artisan,- now it is a claim for a special advantage*" [24]. He proceeds to extol the virtues of the modern lithotomy methods, precise anatomical knowledge, and methods of securing hemostasis and minimizing postoperative complications. He concludes with the following: "*As we now turn our view to the entire body of our comments regarding our many and successfully performed lithotomies, and based on this judge this new stone fragmentation method, then the most fervent conviction compels us to state: that this new method presents no gain for wither our art or for humanity, and that even in these cases where its usefulness is so highly praised by its proponents, that is with smaller and softer stones it lags far behind the usual lithotomy with respect to ease and safety, degree of pain and danger. Yes, we feel justified to state that with today's high degree of perfection of lithotomy brought about by many years of improvement, an operation we have for a long number of years with favorable results it is high treason against our art and humanity to desire to carry out this difficult, painful method which will never achieve a successful result*" [24].

Civiale could not help but to respond also in the literature entitled *Dr. Civiale's nachträgliche Bemerkungen zu der Lithotritie. In Form eines Briefes an den Herrn Ritter von Kern* [25]. He stated "*…and most recently Ritter von Kern, first surgeon to his Majesty, the Emperor of Austria, felt qualified to completely ban my operation method from the field of surgery. Ritter von Kern is considered an authority in Germany, and so it behooves me to show that he especially in the most important points was deeply in error*" [25]. Civiale included the pronouncement from the Academy of Sciences "*The newly proposed method of Dr. Civiale is not only glorious for the French art of surgery and honorific for its developer but equally calming and consoling for humanity*" [25]. He continues, "*However, you, sir have passed a completely different judgment: you believe yourself bound by duty as you have stated to pick up pen for the honor of our art and our colleagues and for the well-being of humanity to push these new instruments in surgery back into nonexistence and propose yourself as the defender of lithotomy*" [25]. He goes even further with "*The comments which you have made in reference to lithotrity are apparently based on events which you yourself have observed with lithotomy though one should consider that both the operations are of very contrary nature*" [25]. But Kern was not finished yet. He again took up pen and paper in 1828 entitled *Die Leistungen der chirugischen Klinik* [26]. He reproduced his objections in full from his earlier objections to lithotrity without printing one word of Civiale's response. It is a telling development that one of his own former surgical students, Joseph Wattmann, performed the procedure that his professor was desperately fighting against in 1827. He performed the first successful lithotrity at the Surgical Clinic of Vienna, and lithotomy was in peril of extinction [27].

Mr. Henry Thompson

Henry Thompson (1820–1904) was born on August 6, 1820, to Henry and Susannah Thompson who were in business in Framlingham of Suffolk. He was schooled locally with the Rev. Miall, who made a wooden set of surgical instruments with which they operated upon various plants [28]. Henry's mother came from a family of well-known artists, and he appears to have had more than a bit of this talent himself. He would later illustrate some of his own writings, especially the Jacksonian papers he would write. Henry appears to have been influenced by a local physician, Dr. Primrose, and his medical student, Mr. Richard Pechey, and he became substantially interested in medicine. He went to visit the University College in London and listened to lectures by Samuel Cooper and Robert Liston and was hooked. He enrolled as an apprentice to a general practitioner named Croydon and also as a medical student at University College in 1847. In his first year he tied for first place in anatomy, and in the second year he won the gold medal for anatomy and the silver in chemistry. He went on to win a gold medal in pathology and another in surgery. In June 1850 he was elected House Surgeon, and he passed the examination at the Royal College of Surgeons. He gained his MD BS with second place honors but winning the gold medal in both medicine and surgery. He got married on December 16, 1851, to a rising star pianist named Kate Loder. He worked for a good share of his honeymoon on writing his essay for the Jacksonian Prize on urethral stricture disease for which he won in 1852 [28]. He became a fellow of the Royal College of Surgeons of England that same year.

The story regarding his interest in bladder stones and lithotrity supposedly began when his own Dr. Jeaffreson in Framlingham showed Henry a lithotrite in 1845. In addition, the French lithotritist Baron Heurteloup also visited the area to treat a local patient [29]. He traveled to France that same year with a friend and developed a taste for fine French food [30]. In 1853 Thompson was appointed assistant surgeon at the London University College Hospital. He returned to Paris in 1857 becoming a member of the Societe de la Chirurgie de Paris and became acquainted with Civiale who taught him lithotrity. Thompson returned and worked on his own technique. He won the Jacksonian Prize a second time writing on prostate diseases in 1860. By 1862 he was being regarded as the leading specialist on bladder stones in England, and in 1863, he was appointed full surgeon. He rose to professor of clinical surgery in 1866. In 1884 he was named professor of surgery and pathology at the Royal College of Surgeons [28]. He had since going to Paris concentrated his practice on genitourinary surgery [31]. Sir Henry Thompson of University College Hospital became one of the leading urologists of his day. His works included Clinical Lectures on Diseases of the Urinary Organs, Practical Lithotomy and Lithotrity, Tumors of the Bladder, Suprapubic Lithotomy, and Preventative Treatment of Calculous Disease [29].

He built an observatory at his home, Hurtside House at East Molesey, in 1880 and equipped it with large telescopes of the latest design. He subsequently presented these telescopes to the Royal Observatory in Greenwich and paid for another. All were made by Sir Howard Grubb in Dublin. He was also a gourmet starting an evening dinner club at his home number 35 Wimpole Street [28]. Eight men were usually invited for an eight-course meal that began at 8 o'clock, and he called the Octaves. He kept a list of all the guests whom he invited including the following: Charles Dickens, William Makepeace Thackeray, Rider Haggard, Arthur Conan Doyle, Sir John Tenniel, Sir Lawrence Alma-Tadema, Edward VII, and Prince George (later George V). His interests in food and cooking were of course turned into another book about healthy diets [31]. He was a remarkably talented artist, and in his youth he tried to emulate his maternal grandfather's efforts, Samuel Medley. He discovered that as he grew older his talents were improved, and he submitted his 1865 medical-themed painting "*The Chrysalis*" to the Royal Academy of Arts Spring exhibition [31]. In all, Thompson had 13 paintings exhibited at the Royal Academy of Arts. He also helped his wife Kate write a popular book about famous art galleries in Europe [32]. Thompson also began a huge interest in Nanking porcelains which he collected, studied, and wrote a catalogue that was published in 1879 [31].

University College Hospital

In the shadow of St. Bartholomew's, St. Thomas's, Guy's, and St. George's, Henry Thompson took his lithotrity operation and transformed the urinary service. The anesthesiologist of Thompson was Dr. Clover, and he invented a practical evacuator to aid in the removal of stone fragments in 1866 (Fig. 19.3). He utilized a rubber bulb as a means of washing out fragments for Thompson [28]. Thompson was an excellent teacher and lecturer. He eventually published his series of lectures that are especially of interest to us because his lectures on bladder stones center upon the rapid changes taking place in surgery, the controversies, and the potential benefits for patients. We will quote extensively from these lectures here to better clarify the perceptions of a leading specialist on lithotrity and perhaps Civiale's most extraordinary pupil.

He started off for his class of medical students with some thoughts on bladder stones themselves: "*That which is most frequently met is uric acid and its combinations; the second is that in which phosphoric acid is combined with volatile alkali and the alkaline earths; and, lastly, there is oxalate of lime. For all practical purposes those are the three great divisions. Among these, uric acid and the urates form about three-fifths in number, the rest being phosphates, with the exception of about three to four percent of oxalate of lime calculus*" [33]. He continued by discussing the hardest stone to break with lithotrity, that of oxalate of lime: "*The oxalate of lime, or mulberry calculus, I need not tell you, is not originally formed in the bladder, but in the kidney, and it is the hardest in structure and the roughest in external surface of all*" [33]. He provided the students hints on how to identify each stone type and admonished them not to attempt a lithotrity on a large oxalate stone over one inch. He went on to discuss the nuances of sounding with the students and introduced a measuring sound. But he described his favorite method of deciding if a bladder stone is too large for lithotrity: "*There is another way. You may introduce a lithotrite (which gives, however, a*

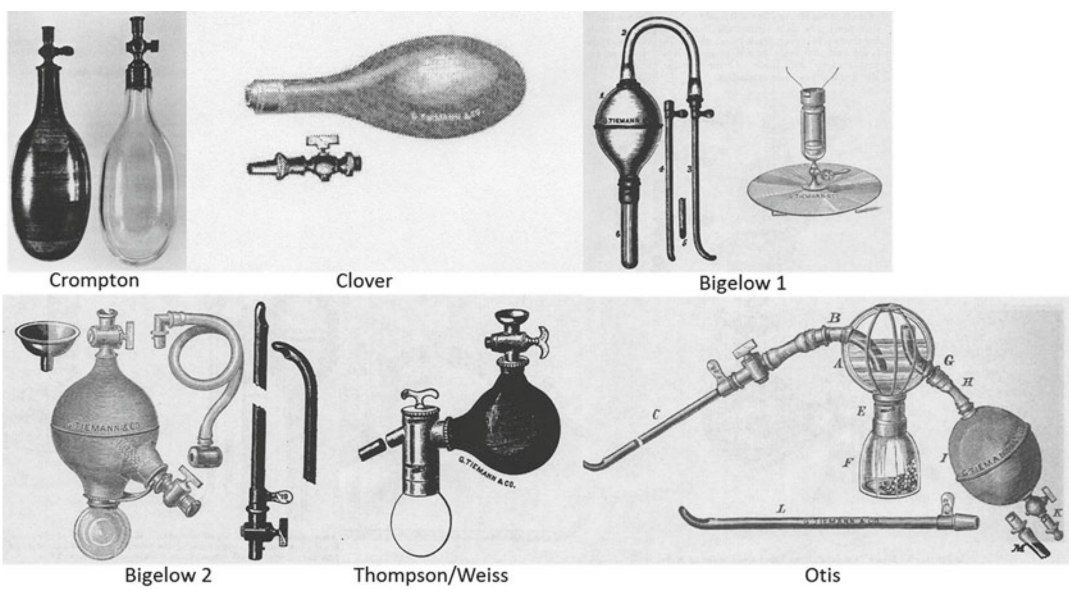


Fig. 19.3 Comparison of various evacuators for removing fragments of bladder stones for visual comparison to Table 19.2

Table 19.2 Evacuators

Inventor	Name	Est. date	Place
Philip Crampton	Detritus bottles	1846	Dublin
Clover	Evacuator	1865	England
Bigelow	Evacuator		Boston
Clover	Improved evacuator		England
F.N. Otis	Evacuator		New York City
French	French evacuator		Paris

little more disturbance to the patient) and seize the stone in two or three directions, so as to ascertain its diameters. At the same time you ascertain its nature. A phosphatic stone gives a very different sound from the others. The specimen before me is dry, and therefore will not give the sound to which I refer. When wet, it is spongy and soft, with a rough surface, and always gives a dull note when struck; whereas the uric acid stone gives a hard ring" [33].

He proceeded to instruct the students in the method of ascertaining the number of stones in the bladder of a patient: "*The number of stones is the next thing. Usually there is only one stone, but occasionally there are more. There is a patient here on whom I shall perform lithotrity tomorrow, who has two rather large uric acid stones in the bladder. The way to determine this point is this: having seized one in the lithotrite, you move it gently in every direction as a sound for others. If you then encounter one on one side and one on the other, you know that there must be at least three stones*" [33]. Now to decide on the surgery, "*Having got all these data, the next important question is, what are you to do? Are you to cut or to crush? You know there are only two modes of removing the stone. You must either make an opening sufficiently large to admit of its withdrawal, or you must crush the stone into very small fragments, so that they may be expelled by the natural passage [note: prior to Bigelow]. It was less important to make a diagnosis of all these points, when we had but one operation-namely, that of cutting. Formerly whether the stone was large or small, the patient was always cut. There was no other way of removing it. Now that we have two operations, it is very important that we chose the right one; because let me tell you, if you do not determine pretty accurately the characters of the stone and select the right operation, you may do more harm than if you cut every patient [shades of Napoleon III]. If you crush the very large stone, and cut for the very small one, you will have greater mortality than if you simply resorted to one operation of cutting in all cases [the argument of Vincenz Kern]. When lithotrity was first introduced, it was rather a clumsy operation; and when the cases were not judiciously selected, when the surgeons rushed without making a diagnosis of all of these points- crushed stones that ought really to have been cut, and left for cutting stones which might have been crushed- the entire mortality resulting from operations for stone was greater than previously, when every case was cut* [now Velpeau]. *I cannot give you a stronger argument for the necessity of apportioning the operations judiciously*" [33].

We should leave Mr. Henry Thompson with some final words of wisdom, though we shall return to this truly monumental figure in the history of stone disease when the next challenge presents itself to bladder stone therapy: "*I hope you will live to see the day when lithotomy for adults will disappear. I do not suppose I shall; but I do expect to live to see one thing, and that is, lithotomy becoming very much rarer than it now is. You certainly will live to see it one of the rarest operations. I do not say that I look forward to that with any particular pleasure; for it is a good operation, demanding all the skill, self-command, and force of a man. It is one of the best practical test of a good surgeon, and, looking at it from that point of view, one cannot desire it discontinuance; but it will disappear, most assuredly; and as it will be for the benefit of humanity that it should, we must acquiesce in the result*" [33].

Thompson and Royal Stones

> "*To operate on one Emperor is unusual- to operate on two one might consider an extravagance.*" [34]
>
> —Ellis, Harold

Thompson had an enormous practice and gained a great European reputation when he was asked to consult on Leopold I, King of the Belgians, who was visiting Queen Victoria. Leopold became the King in 1831 and was the uncle to Queen Victoria when he came to visit here at Osborne. They traveled to Buckingham Palace in London when Leopold developed bladder symptoms which he had sporadically over the past 3–4 years. Sir James Clarke was consulted who apparently knew the King from previous illnesses was called initially, and he called Sir Benjamin Brodie, the Queen's surgeon. It was Brodie who first advised the King to return to Brussels and to consult with Civiale. Clark was a patient of Henry Thompson and called him to the palace to see the King. Thompson also deferred the therapy to Jean Civiale with whom he had trained in the summer of 1858 at the age of 38. In March of 1862 Civiale performed the first of three or four lithotrities his lithontripteur over 3 months, but a larger stone was discovered, and the King's condition deteriorated by December [35]. This is when Bernhard Rudolf Konrad von Langenbeck (1810–1887) from Berlin was consulted who painfully repeated bladder explorations, probably sounding Leopold, but he was released in March of 1863.

Now Sir James Clark strongly recommended the return of Thompson who was called again to visit the King in Brussels. Thompson had new instruments made and took his trusted anesthesiologist Dr. Clover to administer an inhalational agent to the King. They arrived at the Palace in Lieken on May 18, and the King was now aged 73, and the King allowed Thompson to sound his bladder again. Thompson wrote his wife at this time "*I slept only 1 ½ hours last night, between 5 and 6 a.m. I took too much coffee and couldn't sleep, and then I got thinking about my case and I got horribly anxious about it in the night. No one knows how anxious, but those who are placed in like circumstances*" [34]. On June 1, 1863, Thompson sounded for the stone, discovered what he believed to be the stone. He arranged a second sitting for the 6th and brought out the new lithotrite and crushed the stone: "*We saw the King at nine. I injected the bladder with water at H.M.'s wish, having drawn off the urine. I then introduced very carefully the sound and turning to the left, instantly found the hard body. I struck it hard and got again the dull note…I withdrew the sound, introduced the lithotrite with plane blades and turned to the left. I found nothing, to the floor, found nothing but grazed it in the middle line first position and caught it by short diameter crushing it twice. My blades were full, I screwed home tight and withdrew them full with a good quantity of phosphatic debris. After waiting 15 minutes…I injected again at his wish, withdrawing first the water- no blood and introduced again the same lithotrite in the same position and with the same result. A good quantity is now removed. It is what would be an excellent result in any case. Slight trace of blood this time. Pain not much*" [34]. A second sitting was undertaken about 4 days later, and the King made a rapid and improved recovery (Fig. 19.4a). He returned from his 26-day stay in Brussels with a fee of 3,000 lb. He returned 1 year later for a week's duration in follow-up and received another 1,000 pounds. It was a very good year for Thompson; his textbook *Practical Lithotomy and Lithotrity* was released [31]. In addition, Thompson sent his old master, Civiale, a note thanking him for all of his successes. He was appointed surgeon extraordinaire to the King, and the title was maintained by his son, Leopold II, and he was later knighted by Queen Victoria in 1867 [34].

In 1870 Thompson was asked to operate on the much sicker son of Louis Bonaparte (the brother of Napoleon I), Charles Louis Napoleon Bonaparte better known as Napoleon III. His stone symptoms had been ongoing for many years prior to consulting Thompson, possibly in 1856 [36]. In 1864 he had severe bladder pains and gross hematuria while in Switzerland. By 1869 his health was declining, and he was never without urinary infections and urinary retention relieved only by catheterization. On July 1, 1870, a major consultation were called to see Napoleon at Tuileries; present were doctors Nélaton, Ricord Fauvel, Sée, Baron Corvisart, and Dr. Conneau who was his private physician. Conneau wrote up the formal report on July 3, 1870, stated that the emperor had at least four episodes of severe colic and hematuria, but with the outbreak of the Franco-Prussian War, the medical record was suppressed. On July 19 war was declared and Napoleon assumed command of his troupes, but

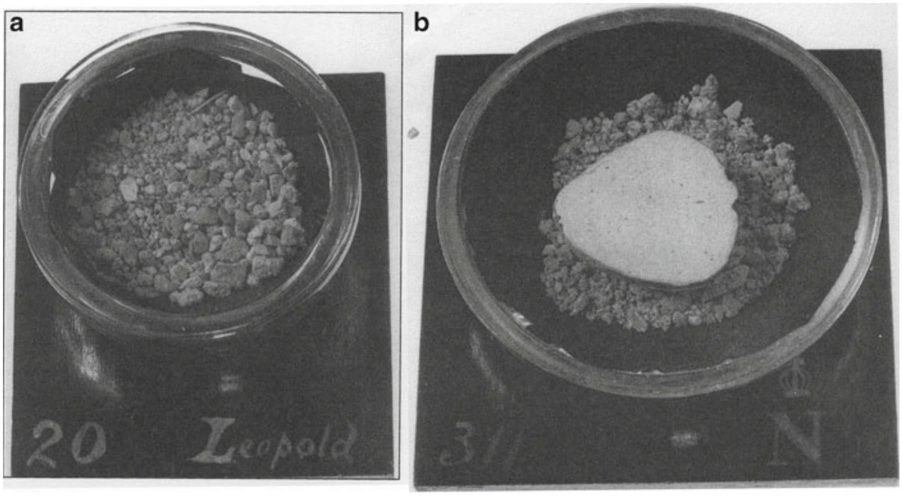


Fig. 19.4 (**a**) King Leopold I, bladder stone fragments after lithotrity, (**b**) Emperor Napoleon III, stone fragments and the remaining ½ of his bladder stone. Both are courtesy of the Hunterian Museum, the Royal College of Surgeons of England

he was often afflicted with severe suffering. He was captured with his army on September 2, and he was requiring catheterization twice daily. It was reported that at Sedan, "*he exposed himself to the enemy's fire, but his bravery may well have been a death-wish to escape the tortures of his stone*" [34]. On July 19, 1872, Thompson was first consulted along with Sir William Gull from Guy's Hospital. The ex-emperor allowed Thompson to examine his prostate but refused at first to be sounded.

Sir James Paget was also called, and he urged Napoleon to allow Thompson to sound his bladder, but again refused. Nearly 2 more months passed and Sir Henry Thompson and Gull were recalled on Christmas Eve, Napoleon was passing purulent urine and desperately agreed to Thompson's surgery. On December 26th Clover anesthetized the emperor, and Thompson sounded for what he believed to be a stone the size of a date. He advised lithotrity and then returned to London. This procedure was scheduled for Thursday, January 2, 1873. Dr. Clover again induced anesthesia, and Dr. Thompson used his flat-bladed lithotrite: "*The stone, which appeared to be chiefly phosphatic, was crushed freely and as much debris as possible was removed by three or four introductions of the instrument*" [34]. There were bleeding and considerable pain following the procedure, and the emperor showed signs of fever and chills. He got worse over the next 2 days with frequency, dysuria, and gross hematuria. On Monday, January 6, a second sitting was recommended, and large fragments of stone were noted impacted in the urethra, and these were crushed. By Tuesday and Wednesday Napoleon was now septic and incoherent, and a third session was planned for Thursday if the patient improved, but his health continued to decline, and he died on January 9, 1873 [37]. An autopsy was performed that revealed the kidneys showed gross pyonephrosis, and within the bladder itself was half a calculus that weighed three quarters of an ounce (Fig. 19.4b): "*Drs Conneau and Covisart called upon him [Thompson] once more in Wimpole Street and presented him with a checque for two thousand pounds. Thompson pointed out that he had only given service for half of one month originally mentioned and consequently insisted on accepting only half the fee*" [34].

Early American Lithotrity

It did not take long for the methods of Civiale to reach the rest of the world. Americans had been for some time already making the journey to Europe for advanced training in medicine and surgery. Philip Syng Physic was one such student who initially spent time with John Hunter in London. He was fully aware of the changes occurring in Europe and apparently well aware of Civiale's success. He notably tried to perform a lithotrity in Philadelphia in 1824 without success [38]. John Rhea Barton followed suit and also failed at the Pennsylvania Hospital since both tried to use American-made copies of Civiale's instruments that were poorly constructed. Valentine Mott, however, a professor of surgery at Columbia College, purchased an original Civiale instrument, but he also failed to successfully break the stones of his patient. René La Roche was next up; he had read and translated the 1824 report by Percy and Chaussier of the Royal Academy of Medicine on Civiale's new method. He also tried to perform a case using American-made instruments and also failed. This prompted La Roche to travel to Paris himself and observe M. Civiale in 1828 [38]. American physicians, it seems, were enthralled by the new method and followed the news of successes such as the first lithotrity in Vienna by Professor Wattmann in May of 1827. Many articles appeared discussing the vigorous debates between Civiale and Velpeau from Paris which kept the New World physicians quite entertained [39].

The first operation of lithotrity performed in the United States utilized Dr. Jacobson's instrument by Dr. Depeyre in New York in October of 1830. The only sources about this pioneering surgeon come from Dr. Jacob Randolph who noted he was a French surgeon living in New York [38]. His first patient was a partial success; he also had an American-made instrument, his instrument maker modified the device, and the patient had "sittings" in November and December then cured. Depeyre also utilized other instruments including Civiale's but eventually switched to the modified Heurteloup device. The second successful lithotrity occurred in Petersburg, Virginia, and was reported on May 20, 1832, using a Civiale instrument [40]. This case is notable because he drilled through the stone three times with the stone in the trilabe and then crushed it using the device. This procedure was done in 20 min with no second sitting necessary. Over the next 3 days, the patient passed 65 grains of stone fragments. The third case was reported by Randolph in September of 1824 where he claimed to be the first lithotrity in the United States (in error of course). But Randolph did report the first series of lithotrities in 1834. Randolph was the son-in-law of Dr. Physick whom we've discussed in the section on lithotomy and who trained with John Hunter in London. Physick first witnessed the successful application of lithotrity declared that "*A statue should be erected in honor of its inventor*" [34]. One wonders if he was thinking back on his famous bladder stone suffers Benjamin Franklin and the fourth Chief Justice John Marshall (1831 reportedly over 1,000 bladder stones removed by perineal lithotomy) [41].

We have briefly met James Mills Bush in the previous chapter on lithotomy. He was born in Frankfort, KY, in 1808 and attended college in Danville graduating in 1828. He was regarded as a witty, genial, and dignified individual; he neither smoked nor drank. He apprenticed with Dr. Goldsmith in Louisville, KY, prior to attending Transylvania Medical College in 1830. At Transylvania he developed the reputation for outstanding scholarship in anatomy. He was also attracted to the work of the professor of surgery, Benjamin Winslow Dudley [42]. He became the prosector of anatomy, and by 1837 he was asked to become the adjunct professor of anatomy at the medical school and published his An Introductory Lecture to the Dissecting Class of Transylvania University in 1840 [43]. In 1839 Bush traveled to Paris and London to increase his surgical knowledge, like his mentor Dudley. He returned with numerous books and instruments, especially regarding the newest methods of lithotrity and began to help with the bladder stone work of Dudley. He was appointed full professor of anatomy by 1844. Dudley moved with some of his associate professors in 1850 to

Louisville to establish the Kentucky School of Medicine but returned to Lexington and the Transylvania Medical School in 1853. The instruments that Bush acquired in Paris and London were put to good use in Lexington. He performed 97 lithotomies with two deaths and 210 lithotrities with only four deaths. In addition, he and Dudley began to document and record each stone case with chemical identification of the concretion which was performed by the professor of chemistry Dr. Robert Peter [44]. He removed perhaps the first cystine stone in America in the 1840s. He died on February 14, 1875, of diabetes.

Reuben A. Vance (1845–1894) was surgeon from Ohio, born and raised in Gallipolis. He studied medicine at the University of Michigan and Bellevue Hospital. He went abroad to advance his surgical skills and knowledge like so many young surgeons of his era. He began his practice in New York City but returned to Ohio. In 1881 he became the chairman of surgery at the University of Wooster (later the Case Western Reserve University School of Medicine). He was a consultant surgeon at St. Alexis Hospital till his death in 1894. He was a proponent of lithotrity and readily adapted the litholapaxy techniques of Bigelow (whom we will meet next) as well as his lithotrite and evacuator in 1880. He died of typhoid fever in 1894 [45].

Dr. Bigelow

Henry Jacob Bigelow (1818–1890) came from a family of surgeons from Boston. He was born on March 11, 1818. Bigelow graduated from Harvard Medical School in 1841 and was determined to follow in his father's (Jacob Bigelow) surgical footsteps [46]. He went to Paris for postgraduate surgical training. Upon his return after several years in the French capital, he joined John Collins Warren and James Jackson at the Massachusetts General Hospital and faculty of Harvard Medical School where he remained for 33 years (1849–1882) [47]. Bigelow was described as "*a brilliant operator, fearless, full of expedients, ingenious, dexterous, cool, alert, and with a dramatic style that dazzled the novice*" [47]. Professor Bigelow was a major advocate for anesthesia after he was a personal witness to the first administration by Morton in the Massachusetts General Hospital in 1846 [48]. Bigelow had been following the techniques of others and was acquainted with attempts at evacuation of fragments (Fig. 19.3). Bigelow was a strong proponent of research and innovative methods of surgery: "*Do not identify surgery with the knife, with blood and dashing elegance. Distrust surgical intrepidity and boldness. The province of surgery is to save and not to destroy, and an operation is an avowal of its own inadequacy*" [48].

Bigelow appears to have a philosophical turn to his writing, he began his classic treatise on litholapaxy as follows: "*When Sydney Smith asked, 'What human plan, device, or invention two hundred and seventy years old does not require reconsideration?' he would no doubt have regarded with favor an occasional reconsideration of the theory and practice of medicine and surgery,- especially in view of the current belief that their traditions had been kept alive and their rules prescribed in part by authority*" [50]. He continues his introduction by praising Civiale, "*Civiale was among the first to inculcate the excessive susceptibility of the bladder under instruments*" [49]. He proceeds by pointing out the problems currently with lithotrity, "*As a rule, there is little difficulty in it. The stone is readily caught and broken into fragments, of which a few are pulverized; a large-eyed catheter is the sometimes introduced; a little sand and a few bits of stone are washed out; after which the patient is kept quiet, to discharge the remainder and await another sitting*" [49]. Now it is time for a reality check; he begins to question the tradition and what really is the fate of the patient: "*On the other hand, it is not always safe…It may happen that during the succeeding night the patient has a chill,…These symptoms may insidiously persist rather than abate. Others may supervene. The surgeon vainly waits for a favorable moment to repeat his operation; it becomes too evident that the patient is seriously ill, and it is quite within the range of possibilities that in the course of days or weeks he may quietly succumb*" [49]. He continues by discussing the need for the utmost gentleness, dexterity, and experience to guide the lithotrity. He recalls watching how Civiale introduced his instrument most gently and how he would limit his lithotrity to between 2 and 5 min: "*The like solicitude seems to have led Sir Henry Thompson, in his admirable and standard work upon this subject, to assign two minutes as the proper average duration of a sitting,- a period which his exceptional skill has often in his own practice enabled him materially to reduce*" [49]. He has now arrived at his premise that with the advent of anesthesia, he can rapidly crush all of the stone and remove all of the fragments in just one sitting which he believes is ultimately safer for the patients. He then proceeds to quote all of the current literature on lithotrity where the evacuation of fragments is decried including Sir Henry Thompson's own textbook [31]. He concludes this section by stating "*In short, the 'evacuating apparatus' and the method hitherto employed do not evacuate. This fact is beyond question*" [49].

Now Bigelow was aware of the recent work by Fessenden N. Otis in New York City on the actual caliber of the urethra that proved to be much larger than people had thought, average 32 mm in circumference [50] (Table 19.3). Bigelow therefore increased the size of his instruments thus was able to remove larger pieces faster in adults. He states "*My evacuating tubes are of thin silver, of sizes 27, 28, 29, 30, and 31 filière Charrière, respectively*" [49]. He is fully aware that this is much larger than Thompson is utilizing which was No. 14 or 25 Charrière. H.J. Bigelow presented his work on what he called litholapaxy in 1878 [51]. In this technique all fragments were attempted to be removed at one setting under a general anesthetic. Bigelow's original contribution was the modification of the lithotrite and his development of an evacuator to remove fragments with a handheld device. He had removed the biting teeth from the female portion of his lithotrite, which in fact probably reduced the efficiency of his instrument in comparison to Sir Henry Thompson's. In his manuscript he presented his initial experience with 14 cases of bladder stone under ether anesthesia for 1–2 h without the detriment to the patient [51]. He presented his improved evacuator for stone debris in 1882 [52]. This was the article that probably triggered the response by Sir Henry Thompson which we'll get to momentarily: "*A hinged or other valve-strainer at the mouth of the catheter, if it opens to allow the water and the débris to pass through, works well enough as a substitute for the tube-strainer. The catheter then opens directly into the bulb, and the route is the shortest possible one. But the tube-strainer is much more simple, and the two inches which it adds to the length of the catheter are quite unimportant. In fact, the usual length of the catheter itself might be reduced two inches to shorten the route if desired. For strainers and strainer traps, see THE LANCET, Sept 24th, 1881. As there described, they are used in pairs, one protecting the entrance of the bulb, while the other, furnished with a valve and placed at the head of the catheter, acts as a trap. The former, for reasons already given, is not always advantageous, but an effectual catheter-trap to arrest returning fragments is necessary*" [52]. The single session technique was rapidly adopted by others, and Bigelow was invited to London in 1881 where he demonstrated his instruments and was made a member of the exclusive London Clinical Society. He was likewise invited to become a member of the French National Academy of Medicine and received the Argenteuil Prize in 1882. Harvard awarded Professor Bigelow its highest honorary degree later that same year, when Bigelow became LL.D. Keegan and Freyer became huge supporters of Bigelow's technique operating on large numbers of bladder stones in India [53].

The relationship of science and development of methods is clearly illustrated in Fessenden

Table 19.3 Fessenden Nott Otis's measurements of the adult male urethra

Circumference midway of the Penis	
Of penis	Of urethra
3 in., or 75 mm	30 mm, or more
3¼ in., or 81 mm	32 mm, or more
3½ in., or 87 mm	34 mm, or more
3¾ in., or 93 mm	36 mm, or more
4 in., or 100 mm	38 mm, or more
4¼–4½ in., or 105–112 mm	40 mm, or more

Nott Otis (1825–1900) and the abilities of Bigelow to take advantage of his work in Boston, yet, Otis also took advantage of Bigelow's work in Boston [54]. Otis in turn published his "*A simplified evacuator for the removal of debris from the bladder after lithotrity*" [55]. He was born in Ballston Springs, NY, on March 6, 1825. Otis studied art in New York and was a teacher of drawing and perspective before entering medical school. Upon graduating in 1852, he served as ship surgeon for the Pacific Mail Steamship Company from 1853–1859. In 1860 he returned to NYC, established a medical practice, and published *On the Structure of the Male Urethra* which included drawings by Otis [54]. Otis was active as an early genitourinary surgeon in New York City, and he investigated the use of a new simplified evacuator for stone debris and published a manuscript in 1883. He noted that "*Had Clover, whose catheter had a calibre of only 21 of the French standard, (about 12 English) or Mercier, employed larger catheters, (between 25 and 31 French- 15-20 English) they might have evacuated the bladder completely*" [55]. His evacuator is quite similar to those used in a modern urologic surgery suite (Fig. 19.3). He does add one interesting trick of the trade, "I*n order to show how completely the debris is removed from the influence of the current which returns to the bladder, colored solution may be placed in a bottle, the receiver filled to the brim with glycerine, and attached to the reservoir*" [55]. An ingenious demonstration if ever one has been described. Otis died in New Orleans on May 24, 1900 [56].

Thompson on Bigelow

On January 20, 1883, Sir Henry Thompson responded to the professor from Harvard in a letter he wrote to The Lancet. We will quote this letter in its entirety [57].

> *"Sir,- I should not trouble your readers with any remarks on Professor Bigelow's article on a 'Simplified Evacuator' had he not made, relative to my instrument, statements which are extremely inaccurate. On this account alone it is that I am compelled, with more reluctance that I can describe, to contest any question with my respected friend, the Professor of Harvard.*
>
> *First, he describes and draws an aspirator of mine, which he says I have 'lately abandoned'! So far from having done so, I rarely operate without it, and use it nearly as often as the more recent model.*
>
> *Next, the drawing of this aspirator is tended to prove that its action is do defective as to return into the bladder a large portion of the debris already removed. I have, moreover, long known that Professor Bigelow has been in the habit of exhibiting one of my aspirators for the purpose of publicly illustrating its alleged defects (with bits of coal and water). I do not make any great complaint of this, although it is a mode of controversy to which just exception might be taken.*
>
> *All I have to say is this, that nothing is easier than to use another man's instrument, in that man's absence, so as to make the instrument appear inefficient. But it is not so in my hands. Had Professor Bigelow ever seen me use it- as scores of his compatriots have- he would know that, if properly used, there is no reflux of debris into the bladder. The best instrument in the surgical armamentarium may be misused, and grossly too, and such is the fate of mine in the professor's hands if he meets with the result which he is at such pains to publish to the world.*
>
> *I have performed the operation of lithotrity at one sitting more frequently, probably, than any living operator; and I am delighted with it. Will anyone say- and there are abundant witnesses- that is not a rapid and complete proceeding in my hands? How could that be possible if my aspirator is so defective?*
>
> *And now I have only to congratulate Professor Bigelow on his present search for 'simplicity.' He well knows that I regard his suggestion to remove the stone at one sitting as a great advance. But his first instruments were a return to the time of Heurteloup! After years of patient experience, the mechanism of both lithotrite and evacuator had become marvelously simple and efficient. This simplicity he disturbed, disastrously, for a time; exhibiting the elaborate and costly apparatus at the Congress here in 1881, wholly useless to the practical lithotitist. He could not see that not one new instrument was required to carry out his excellent idea. As we were to attack larger stones, we wanted larger and stronger instruments- that was all. Clover's bottle, a little modified perhaps (as I suggested last January in The Lancet) is as good as, if not better than, any, and I still often use it. Only make it larger than before, and attach a larger evacuating catheter, when you want a larger, not otherwise. All the perforated tubes and strainers get so blocked with debris (as I found long since) in the human bladder- not with coal in water- as to be practically useless there.*

I am heartily sorry to have been compelled to reply in a spirit of criticism, but the statements and the mode of proceeding referred to above rendered it impossible for me longer to remain silent. I am, Sir, yours obediently,

Wimpole-street, W., January 1883 Henry Thompson [57].

Conclusions

"*It is not possible to be ignorant of the end of things if we know their beginning.*" [58]

—Thomas Aquinas, Summa Theologica

As Civiale continued with success in his practice at the Necker, right next to him was another young visionary by the name of Desormeaux's who by 1835 was trying to peer into the urinary bladder using a gas lamp endoscope. It has been recorded that Civiale ridiculed this young pioneer and thought that cystoscopy was not only tiring for the patient but could give rise to serious accidents. He had no capacity to open his mind any longer to the truly innovative; Maximilian Nitze (1848–1906) was to be working on improved cystoscopes in 1876; Edison would patent his incandescent light bulb in 1886, and it would be applied to cystoscopes shortly thereafter. Röntgen discovered X-rays in 1895, and within 1 year the first radiographs of stones were being taken, some again at the Necker Hospital. With the size, number, and exact location of stones becoming known, it was just a matter of time before some new method of destroying stones would be developed as imagined by both Franz von Paula Gruithuisen (electrohydraulic lithotripsy), and Jean Civiale would soon become part of the armamentarium of modern stone surgeons. Civiale recalled efforts to improve things later in his life and it is worth quoting him in detail:

"*For forty years the professors of the Surgical Clinic of the Faculty of Medicine of Paris have been practicing lithotomy, and during that time have contributed nothing to the theory and practice of this procedure. On the contrary their instruction has inculcated ideas and technique contrary to the lessons of experience. By an error perhaps never equaled in the history of surgery, these learned professors have constantly rejected my instruments and my methods, the only ones by which one succeeds certainly, and by preference they have described in their lectures and their elementary theses other instruments and other technique the usefulness of which has not been proved.*" [59]

Albert Einstein would also envision another modality that would replace all others in the management of many stones regardless of location, highly energized single wavelength coherent light. But these are topics for another chapter. But all of the massive efforts by these pioneering surgeons to minimize the trauma on patients already suffering from a horrific disease would be rapidly replaced by the methods of Desormeaux, Nitze, and many others that were accelerating human knowledge at an increasing rapid pace.

The endoscope and X-rays got rid of the blind nature of these procedures, so at the turn of the twentieth century, there was almost no need for the pure skill of blind lithotrity and complete evacuation [61]. A lens or an X-ray could simply tell the surgeon whether the stones were completely removed or not. In addition, there were complications of blind litholapaxy, and the bladder could be easily injured especially in beginner's hands. Max Nitze in Berlin by 1891 was trying to develop an endoscopic lithotripter utilizing a variation of Heurteloup's. He struggled with designs for years because of size constraints and materials. Fenwick in England tried to bypass the urethral problem and developed a trocar cystoscopic system which he had made by Leiter in Vienna [61]. Fenwick went one better; he also developed clay models so that he could simulate his endoscopic attempts at lithotrity and a variety of other procedures. George Robinson of Newcastle recalled the attempts by Gruithuisen to utilize the energy of an electrical spark to break stones tied again in 1855 to reproduce this method of using energy to destroy stones [62]. Leopold Caster in Berlin also tried to improve the Nitze system with better crushing graspers to improve the endoscopic lithotrity in 1895 [63]. George Walker did improve an endoscopic lithotrite that could generate 175 lb of pressure in 1907 [64]. Walker discusses the available options and points out the advantages of an endoscopic technique and compares his instrument to that of Nitze, Bierhoff, and Casper. To quote an early author, "*The advantages of endoscopic lithotripsy over blind lithotripsy are easy to understand. Grasping the stone and fragments can be performed under constant visual control and crushing can be repeated until all of the fragments are easily aspirable through the catheter*" [64].

We have discussed the rapid evolution of lithotrity to litholapaxy and a single sitting procedure, but these were pure testimonials to surgical skill and prowess, essentially as prophesized by Bigelow [65]. In 1921 a series of 153 cases of litholapaxy were reported from the Mayo Clinic with a mortality of 1.3 % and a recurrence rate of 7.8 %. This was compared to 395 cases of suprapubic lithotomy recurred only 4.5 % because the prostate could be removed in those cases synchronously [66]. Soon an endoscopic transurethral resection of the prostate (TURP) could minimize even the risk of the suprapubic prostatectomy when there were associated bladder stones. Thompson also from the Mayo Clinic reported a series where combined TURP and litholapaxy could be safely performed in one sitting with only one death out of 154 consecutive cases (0.6 %) [67].

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20 Imaging the Beast: Sounding, Lithoscopes, and Röntgen Rays

Introduction

> "*The restricted and ordinary meaning of sounding is, the introduction of an instrument through the urethra into the bladder, to obtain evidence, by the touch or hearing, of a calculus being present.*"
>
> John Green Crosse, 1835 [1]

Stone disease before the advent of Wilhelm Conrad Röntgen was done by careful history and physical examination. Confirmation was possible only with bladder and urethral stones however. This confirmation also has an interesting history; it was typically performed by itinerant lithotomists and later by skilled surgeons. The technique to identify a stone was called "sounding" and the name essentially is self-explanatory. The specialist would pass a typically metal instrument transurethrally in a male or female suspected of stone disease and listen intently for the contact with a concretion that could create the metallic "clink" associated with a stone (there were occasional porcelain sounds; glass too makes vibrant tone but would add danger to the procedure). A more skilled practitioner was capable of gathering information on the size and number of stones in the bladder. According to Gross, "*Sounds vary in their construction, in their size, and in the materials of which they are composed. The best are solid, made of steel, and plated with nickel, with varying degrees of curvature. For an adult, the length, from one extremity to the other, should be about twelve inches, of which two inches and a half should be allowed for the handle*" [2].

We have previously noted that stones are mentioned no fewer than in 24 passages of the Hippocratic dogma. Stone formation is discussed in six (25 %) of these aphorisms [3]. Now in the Hippocratic corpus entitled On *Air*, *Waters*, and *Places*, the Hippocratic writer warms to the theme of stone disease [4]: "*But if the belly is liable to fever the same must be true of the bladder becomes inflamed and does not allow the urine to pass which instead becomes heated and condensed. The finest and clearest part is separated, passes through and is voided. The densest and cloudiest part is gathered together and precipitates in small pieces at first then in larger ones. The gravel formed is rolled round by the urine and coalesces to form a stone. When the water is passed this falls over the neck of the bladder, and being pressed down by the pressure of the urine, prevents the urine from being passed. Great pain is thus caused. As a result, childrens suffering from stone rub or pull at their private parts because they think that in them lies the cause why they cannot make water*" [4].

Joseph Covillard from Lyons quoted a patient who could feel the calculi shake in his bladder; nine stones were subsequently removed [5]. The great Vesalian anatomist from Padua, and teacher of William Harvey, Fabricius ab Aquapendente, also noted that when calculi are numerous, as well as considerable size, they have been felt by the patient to move against each other: "…*stepitum in motu aegrotantes persentiunt*" [6]. Gross discussed the symptoms as well but goes on to state, "*When the symptoms above described are*

M.E. Moran, *Urolithiasis: A Comprehensive History*, DOI 10.1007/978-1-4614-8196-6_20,

all present, or even when several of them are absent, there is a strong probability that the patient is laboring under stone of the bladder, and this probability is converted to certainty, when the surgeon is able to feel and hear the foreign body" [2].

The Sound and the Fury

Though the title has been borrowed from William Faulkner's best selling classic novel of 1929 about a Southern Family that is imploding [7], he too borrowed the idea from Shakespeare's *Macbeth* in the soliloquy of act 5, scene 5 [8]:

Life's but a walking shadow, a poor player
That struts and frets his hour upon the stage
And then is heard no more: it is a tale
Told by an idiot, full of sound and fury,
Signifying nothing.

Imagine if you can being a patient in the Middle Ages—there are no narcotics; no anesthesia is even possible, only intoxication; and if you are extremely lucky, the practitioner who is called to see washes his hands and instruments. The pain of a bladder stone is immense, and desperation is the only pathway that would deliver you to the hands of a lithotomists. Prior to proceeding with the torture of surgery, you must first endure the passing of a metal rod through your penis in order to probe and make sure that a stone is present. Though itinerant lithotomists were probably not all idiots, we do glean from some classical sources that they might not have been too far removed from that lowly status. Let's recall the statements from the eminent physician/writer Sir Thomas Browne on surgeons. In 1679 he wrote, "*The ignorance of chirurgeons as to the chirurgical operations creates so many mountebanks and stage quack-salvers*" [9].

Tommaso Alghisi (1669–1713) was a lithotomist who discussed the art of using the sound. Lithotomists had already explored for centuries different types of implements for passing into the bladders of humans to insure that a stone was present [10]. Tommaso was born on October 12, 1669, to a master of surgery at the Sta. Maria Nuova and probably apprenticed there. He became a surgeon qualifying to the "barber-surgeons" on April 25, 1692. He was substantially influenced by the local scholars of Florence, particularly Francesco Redi, and perhaps met Steno. He married Margaret Lombardi in 1697, and eventually they had six children. By 1699 he was appointed as a professor of surgery at Sta. Maria Nuova, and his father died in 1702 leaving him in charge of surgery. In 1708 the University of Padua conferred the degree of doctor of medicine upon him [11]. Tommaso created one of the first well-illustrated books on lithotomy using woodcuts of Cosmus Mogalli (Fig. 20.1). There are 16 engraved plates in this treatise, with exquisite drawing of handling of the sound. Alghisi was the pupil of the famous Bellini, and he is given credit for using an indwelling catheter to drain the urine away from the wound following the lithotomy. He used the *Grand Appareil* and became famous and attracted the attention of Pope Clement XI to whom he dedicated his book. Thin flexible myrtle leaf sounds were used by some, while large metal instruments were favored by others [12]. A porcelain probe was described by Auguste Nélaton to identify a lead ball in soldiers in 1862 [13].

We've already encountered John Greene Crosse (1790–1850) during our discussion of Norfolk and Norwich school of lithotomy. Crosse was another surgeon who was interested in the science of medicine and in stone disease in particular. He was born on September 6, 1790, in Suffolk, and he became one of the nation's leading surgeons, specializing in lithotomy. He also was elected as a fellow in the Royal Society, and his son wrote a biography about his father [14]. His book on stone disease was originally an essay that won the Jacksonian Prize for medical writing by the Royal College of Surgeons in London in 1835 entitled A Treatise on the Formation of the Urinary Calculus [1]. He is one of the few lithotomists who talked in detail about the art of diagnosing bladder stones, the pitfalls of diagnosis, and the methods to improve selecting patients for surgery: "*In dedicating a separate chapter to this subject, I wish to take a more comprehensive view, including all collateral methods of gaining information, not only of the presence of a stone*

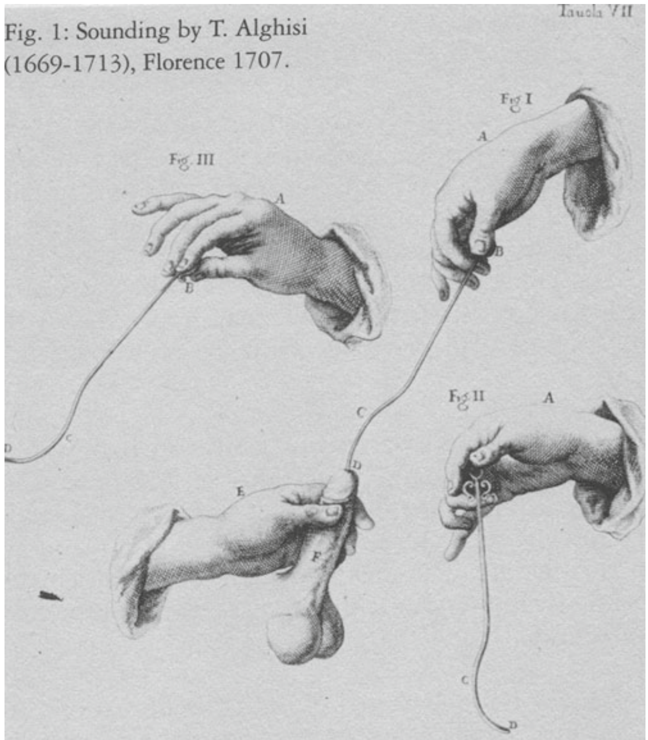

Fig. 20.1 Tommaso Alghisi's illustration of sounding

or stones, but their size, situation, mobility, number and texture" [1]. Crosse has phrased the problem for surgeons of this time, prior to accurate diagnostic methods that would soon evolve into quite sophisticated methods that will finally obliterate the differential diagnosis and allow patients the luxury of knowing what operation will be performed as well as allow more than a substantial margin of success, which will conclude this textbook, when we discuss six sigma and stone disease.

Crosse went into some details about the sounds themselves and the technique of sounding adults and pediatric patients: "*For a general description, we may say, that a sound should be as long as a catheter, and curved for the last three or four inches that it may project into the bladder; it should not be so large as to fill, much less to distend the urethra, but of moderate size, that it may readily be moved backwards and forwards in this passage, and its curved part turned in different directions in the bladder*" [1]. He would continue with some further nuances of the sound and the technique: "*Every surface should be well polished, and the handle, being always intended to suit the operator, should be broad enough to receive the thumb and two fingers, and not small, whatever be the size of the rest of the instrument. It is necessary to have the handle well polished, that the fingers may touch a greater surface, and receive and recognize the most delicate impression; by being wedge-shaped, or thinner at its extremity than next the body of the instrument, it has the advantage of increasing the impression conveyed to the touch by any resisting body, when the instrument is pushed onwards, the most usual and always the first movement to be given it in sounding*" [1]. He quaintly extolled the maker of instruments "*The custom of the instrument-maker in placing his name on the handle, thereby interrupting the smoothness of surface where most necessary to preserve it, should be countermanded, and every instrument so defaced be rejected as imperfect*" [1]. But a lot was at stake, and Crosse was a surgeon who wanted no errors.

He proceeded with the methods of sounding: "*Children are never sounded in the erect posture; but when you have to deal with an adult patient, it will be found advantageous to make the first examination in that posture; in doing this, you should, with as little preparation and alarm to the patient as possible, introduce the sound lightly and gently, with a very delicate hand, endeavoring to steal as it were through the passage, by employing scarcely more than the weight of the instrument to propel it along and elevate its extremity into the bladder, if the operation be thus feelingly and judiciously managed, in nine instances out of ten, when there is a loose stone of any considerable size in the bladder, it falls down to the neck of this viscus, and is felt on the sound first entering*" [1]. He continued to describe detailed aspects of sounding, including a thorough probing of the entire bladder in a systematic fashion. He discussed the ability of sounding with more thoroughness with the patient in the horizontal position (now called lateral). He also talked about the occasional need to sound a person in the knee-chest position or in the lithotomy half-sitting position where the head is elevated to 45°, "*this latter being the method to remove the stone from the neck of the bladder and carry it to the fundus*" [1]. Crosse also pointed out that various lithotomists might use different types of sounds, and he discussed these in some detail. He presented his use of a silver catheter to empty the bladder and how this device can actually be used as a sound. He noted this technique was particularly useful for "*a small stone, brought down to the neck of the empty bladder and pressing against the catheter where the openings are situated, affording an indisputable grating feeling and noise*" [1]. He mentioned the newer gum-elastic catheters that were promoted by Sir E. Home and Sir B.C. Brodie of London, but he has used them and finds them to be inferior to his metal sound technique [15].

Mr. Crosse was able to gather much information from careful examination with the sounding: "*Where the sound touches the stone in different directions, and is found to pass over a large surface of it, you may conclude it is of large dimensions; but when, under the same position of the body, you do not feel it repeatedly, on passing the sound to the same part of the vesical cavity, it likely to be small*" [1]. He next discussed the need for careful rectal examination: "*In every case, before undertaking an operation for the removal of a vesical calculus, the surgeon ought to examine with the finger in ano. In young patients, we can feel through the rectum the whole outline of the bladder, and often tell the size and situation of the stone contained in it. In the adult, examining by rectum enables you to detect a calculus in the membranous or prostatic portion of the urethra, or acquaints you with the size and condition of the prostate gland; and when the finger is long enough, you can tell the state of the bladder, as to tenderness on pressure, and thickness of its coats*" [1]. In modern textbooks of urology, no truer statements on the necessity for the thoroughness of the exam to substantiate the differential diagnosis exist.

Samuel D. Gross's "*Practical Treatise on the Diseases, Injuries, and Malformations of the Urinary Bladder, the Prostate Gland, and the Urethra*" in 1851 also presents a surgeon's view of sounding for bladder calculi [2]. Samuel D. Gross is the surgeon that was immortalized by Thomas Eakin's "The Gross Clinic" painting of 1875. Gross was a pioneering experimental surgeon who rose in fame at the frontier school the Louisville Medical Institute. He practiced surgery there for 16 years before he was lured back to Philadelphia as the professor of surgery at Jefferson Medical College [16].

The Sound of Silence

Since we've already allowed the metaphorical sidebar to Faulkner and Shakespeare, now would be the appropriate time to repeat this pandering for amusement. Paul Simon would turn his music and lyrics of this name into a number one hit single and album in 1964. Simon was eulogizing the assassination of President Kennedy, perhaps more harmonically than what Walt Whitman's *O Captain*! *My Captain*! did for Abraham Lincoln [17]. But the patient's suffering from stone disease and a whole host of other urinary tract abnormalities were not a trifling problem. Diagnosis could not be made by history and physical examination alone. Passing sounds and gauging the information was a skill that not all clinicians could master. A posthumous work a celebrated surgeon Prof. Luigi Valentino Brugnatelli of Pavia appeared in 1819 published by his son, called *Litologia umana*, mentioned this skill set [18]. This work focused on stones, primarily of the bladder, and discusses the differential diagnoses.

John Green Crosse was a skilled surgeon and lithotomists and had taken more than a passing interest in his craft and his outcomes. He was interested in all the aspects of the surgery and the patient. Crosse was not alone in abhorring the possibility of operating on a patient and being wrong. Also in very good surgical hands, the mortality rate for the lateral lithotomy was just around 10 % [1]. Complications included permanent sterility, urinary incontinence, development of an abscess, a draining sinus, or the development of a perineal fistula. The art of sounding was itself risky as exemplified by Samuel D. Gross in his 1876 "*prepare the system for the operation of lithotomy, it is hardly less so, in my judgement, to prepare it for that of sounding. From neglect of this precaution, patients are often subjected to much suffering, and even to great risk. Indeed, there is reason to believe that life has been repeatedly sacrificed in this way. Bad consequences occasionally follow, even when the utmost care is taken. I myself have witnessed very serious effects from this kind of indiscretion, which has been followed by severe cystitis. Sir James Paget has known death to ensue from simply sounding for stone in six instances; and Fletcher, Crosse, Sanson, Civiale, Horner, and other surgeons, allude to similar cases*" [2].

If having a complication from the diagnostic test of choice was significant, it is no surprise that the best surgeons of the era would also be concerned about operating on the poor patient and discovering that there was no stone. Let's turn again to Gross for his thoughts on this matter: "*Although sounding is the only certain method of detecting a stone in the bladder, it is occasionally liable to error. Numerous cases are upon record where a foreign body was supposed to be present, and where the poor patients were subjected to all the pains and perils of lithotomy, and yet no calculus was found, either at the time of the operation or after death*" [2]. This sad outcome was not limited to the average surgeon of the time. Gross continues, "*Surgeons of the consummate skill and the most extensive experience have fallen into this error. Cheselden, the most celebrated lithotomists of his age and country, cut three patients without finding any stone. Blane, Dupuytren, Roux, Crosse, Tyrrell, Cotta, Vacca, Aason, Medoro, Borsiori, Ucelli, and Paget, of Leicester, all operated, expecting to find a stone, where there proved to be none*" [2]. The real incidence is quite possibly higher in less experienced hands: "*Mr. Crosse states that he has notes of not less than eight cases in which the operation was needlessly performed, and to several of which he was an eye-witness. The late Mr. Samuel Cooper, of London, was acquainted with the particulars of at least seven such cases, at two of which he was present. Velpeau says he has a knowledge of four instances, where the patients were subjected to the operation without there being any calculi in the bladder, and I myself am cognizant of at least half a dozen cases in which this mistake was made*" [2].

On the opposite side of operating for nothing, there was also the possibility of miscalculating the size of the stone. Too big of a stone was not doable from a perineal lithotomy, nor could even the best lithotripsy render a big stone into pieces small enough to pass. The sin of omission was possibly better than the sin of commission when it came to bladder stones. Louis Napoleon was the nephew of the great Napoleon of the first empire who has been maligned by Victor Hugo as incomparable to his uncle. He certainly became emperor himself and the marshal of the second empire until his defeat at Sedan on September 4, 1870. But Napoleon III suffered from bladder stones, and his ultimate demise might be attributable to medical mistakes [19]. He suffered from his stones in an era prior to antibiotics, and the attempts at performing lithotripsy were delayed, perhaps too long. Multiple factors have been analyzed by medical historians that include global world politics, the emperor's unwillingness to have treatment, and professional egotism. It is known that the ex-emperor had bladder stones in 1864, though a letter in 1853 stated "*The emperor is ill and suffers from pain, the bladder in particular seems to be affected*" [20]. By 1860 despite multiple medical opinions his condition had deteriorated, and he was only 52. It is believed that the great physician Felix Larrey is the first to really consider bladder stones. Napoleon was finally catheterized by Dr. Guillon in July of 1866, and stone was confirmed. He had to be catheterized repeatedly after this, and each time was associated with a febrile episode. He consulted Auguste Nélaton who catheterized him with a metal catheter that was painful and associated with gross hematuria. The emperor called back Guillon who resumed the catheterization with a softer, olive-shaped resin catheter, and Napoleon approved. By August of 1869, his symptoms were back, and Nélaton, Ricord, Fauvel, Germain, Corvisart, and Conneau were all gathered on July 1, 1870, and his infection was thought too severe and precluded any safe surgical intervention. A few days later the emperor was in Sedan when his armies were routed, and he was captured. Napoleon's forced captivity and rest actually resulted in a brief improvement of his health. In July of 1872, he again relapsed, and Corvisart and Conneau were again summoned. They also called the famous surgeon Sir James Paget (1814–1899) and Sir William Gull who was Queen Victoria's own physician. It was decided to call for Sir Henry Thompson who was considered by many to be the best stone man in England [20].

Sir Henry Thompson (1820–1904) was born in Suffolk on August 6, 1820, and attended London University College and Medical School. He graduated with distinction and married Kate Loder, a pianist who died not long afterwards. He went to Paris to learn lithotripsy from Civiale. He published *Pathology and treatment and structure of the human urethra* in 1852. This was followed by *Health and morbid anatomy of the prostate gland* in 1860. He was considered the best "urologist" in London by the time Napoleon III had significantly worsened. The royal family had requested that Jean Civiale himself be called, but apparently his fee was exorbitant.

Between October and December of 1872, Napoleon's symptoms worsened, and Thompson had to catheterize him and suspected a phosphate stone the size of a date. He was again catheterized under chloroform anesthesia on December 27, 1872, and Thompson used his lithotrite to measure this large stone. He recommended a lithotripsy which was agreed upon for early January. The surgery was begun at 3 p.m. on January 2, 1873, with many medical dignitaries present. Thompson crushed the stone and removed as many fragments as possible. By 6 p.m. Napoleon was febrile but his urine remained clear. He developed increasing difficulty voiding however, and a re-exploration was recommended. On January 6 Thompson discovered a large fragment impacted in the prostate and had difficulty inserting his instrument into the bladder. It soon was evident that only about 1/5 of the stone was removed on the first lithotripsy, and his urine became increasingly bloody. His condition rapidly declined and he died on January 9 at 10:45 a.m. [20]. An autopsy was performed by Dr. Burdon-Sanderson from London University who noted "*The ureters and the renal pelvises are extremely dilated. The left kidney in particular is highly hydronephrotic, hardly any functional parenchyma is left…The bladder still contains a fragment of stone. Judging from its appearance, about half of it has already been removed. There are also three smaller stone fragments slightly larger than a hemp granule. The stone has a total weight of ¾ ounce and measures1 ¼ by 1/5 of an inch*" [21].

Röntgen

William Conrad Röntgen (1845–1923) was born on March 27, 1845, in Lennep, a small town on the Lower Rhine. He trained in the Netherlands but attended the University of Utrecht to study physics. He married Anna Bertha Ludwig of Zürich in 1872; they never had children of their own but adopted a daughter of his brother named Josephine [22]. His first published work concerned the specific heat of gases, and he was also interested in the thermal conductivity of crystals. In 1895 he was studying the

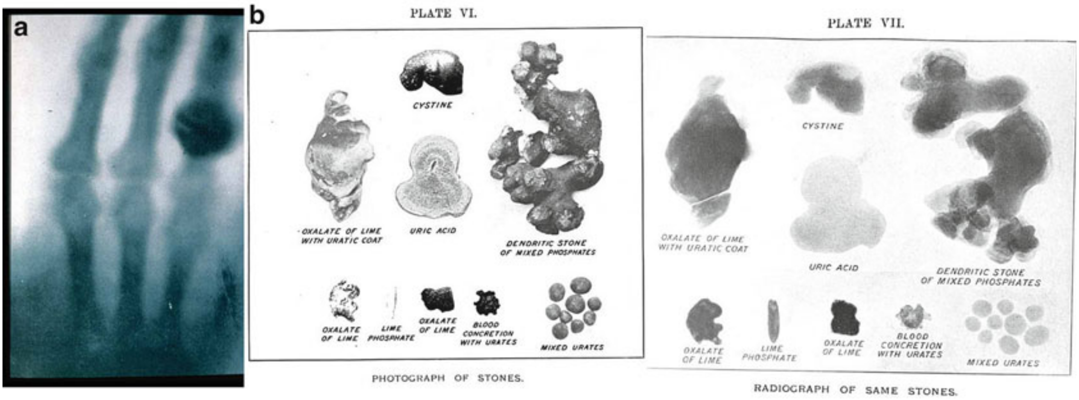

Fig. 20.2 (**a**) Röntgen's famous sequence of X-ray photographs that he mailed to dozens of colleagues in 1896 and (**b**) stones and an early X-ray from Fenwick's textbook in 1908

phenomena accompanying the passage of an electric current through gases of low pressure. He was following leads by many others, including Thomas Edison and Heinrich Hertz. He utilized a tube modified from Sir William Crookes that was initially described by Ruhmkorff. On the evening of November 8, 1895, he discovered that the tubes emitted another type of ray that passed through coatings. In fact he immobilized his wife's hand over a photographic plate and subsequently after developing the photograph noted his wife's bones of the hand with the ring she was wearing as a shadow image. He proceeded to perform subsequent experiments prior to publishing and presenting his findings on December 28, 1895. His paper was rapidly translated into many languages, and *Die Presse*, a Vienna newspaper, heralded the breakthrough on its front page of the Sunday edition: "*A sensational discovery of Professor 'Routgen' of Wurzburg has stirred the imagination of leading scientists*" [23].

Röntgen did more than sit on his idea, however. He proceeded make a series of photographic X-ray impressions and sent them with a copy of his paper to other physicists who he knew were interested in this work. On January 1, 1896, Röntgen wrote to several of his colleagues and enclosed in some cases at least eight images or examples of the very first radiographs (Fig. 20.2a) each marked with the stamp "*Physik Institut der Universität Würzburg*." He included the first of his three papers on X-rays. Röntgen's own attitude on his own work was one of caution. Sir Arthur Schuster a professor of physics at the Manchester University was one of the first English persons to receive this envelope. He noted "*I opened a flat envelope containing photographs, which without accompanying explanation, were unintelligible. Among them was one showing the outlines of a hand, with its bones clearly marked inside. I looked for a letter which might give the name of the sender and explain the photographs. There was none, but inside an insignificant wrapper I found a thin pamphlet entitled 'Uber eine neue Art von Strahlen.' by W C Röntgen*." Soon Shuster would complain that "*my laboratory was inundated by medical men bringing patients, who were suspected of having needles in various parts of their bodies and during 1 week I had to give the best part of three mornings locating a needle in the foot of a ballet dancer*." The firestorm had started, and several textbooks on X-rays were rapidly published [24].

Lithoscopes

At this juncture, though the rapidity of the rise of X-rays showed that astute practitioners were aware of the groundbreaking capabilities of these new rays in diagnosis, there were also skeptics, as there always will be. In 1890, Robert Ultzmann in

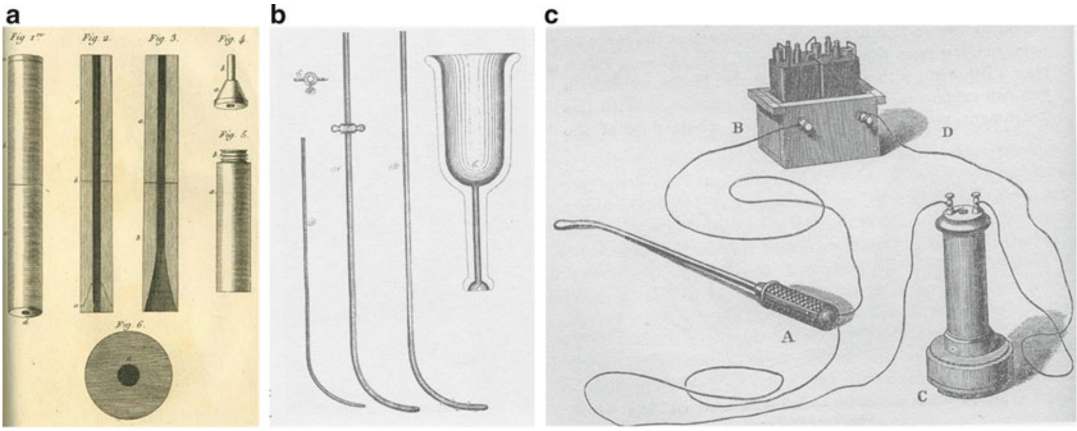

Fig. 20.3 (**a**) Laennec's stethoscope, (**b**) Figure 6 of Carl Joseph Pfriem's lithoscope, and (**c**) Sir Henry Thompson's microphone sound

Vienna unabashedly stated that the identification of bladder stones must still be done with careful sounding [25]. It was in this era of skepticism that alternatives were still applicable and innovative ideas were being tried. René-Théophile-Hyacinthe Laennec was born in Quimper on February 17, 1781. He studied medicine in Paris and worked with Dupuytren and Nicolas Corvisart des Marest. He probably became interested in the magnification of sounds from his mentor des Marest who had championed auscultation in careful examinations. He published his *De l'Auscultation Médiate* in August of 1819 (Fig. 20.3a) [26]. It did not take long for surgeons interested in learning more definitively about the size, shape, number, and location for bladder stones to begin to use this innovative device.

We have discussed John Green Crosse's technique of sounding in some detail earlier. We must briefly return to his remarkable book once again. He was fully aware of Laennec's device and its application. He noted "*The stethoscope placed upon the os pubis, or any where over the region of the bladder, will be found an useful assistant for discriminating the impressions conveyed through the sound; where the impression, as otherwise ascertained, is feeble and obscure, the assistance of this instrument for auscultation should be availed of and may by experience be turned to most profitable account. The surgeon, whilst employing the stethoscope, may move the sound himself or give it into the hands of an assistant, and in either case derive information from the former instrument. Vesical auscultation admits of many more researches and is probably susceptible of valuable improvements*" [1].

Jacques Lisfranc in 1824 used Laennec's stethoscope in an attempt to identify bladder stones. He wrote, "*It is well known, that the famous Desault misdiagnosed a spongy tumor of the bladder as a stone. Moreover, sometimes in patients where section alta was performed, no was found. I believe that the stethoscope will help prevent such mistakes*" [27]. This was followed by another paper in 1836 from M. Francois Moreau an assistant to Armand Velpeau at the L'Hôpital la Charité using an ivory membrane stethoscope to improve on the sounds of bladder stones. Joseph Frederic Benoit Charrière (1820–1865) a Swiss instrument maker reported from Paris on listening through a long catheter with simply his ear at the opening to hear the sounds of contact with a stone [28]. Brooke in London tried to develop an acoustic resonator that consisted of wooden disc with a central hole in which a catheter could be placed. When the catheter contacted a stone the idea was that the sounds would be magnified by the wooden resonator near the ear. Finally, the great surgeon Theodor Billroth (1829–1894) also had an assistant by the name of Heard (no pun intended) who developed an acoustical probe with flexible ear pieces [29].

Carl Joseph Pfriem followed in the wake of René Laennec and those who labored to develop an acoustical device that could more accurately not only identify a stone, but also predict the size, dimensions, and location of these concretions. He was a medical student at the time, so in 1838 he wrote his doctoral thesis entitled "*Das Lithoskop*, *oder Beschreibung eines Instrumentes zur sichern Diagnose der Harnblasensteine*" (The Lithoscope, or the description of an instrument for definite diagnoses of bladder stones) [30]. It is interesting that this young physician was working at the University of Würzburg, the same institution that Röntgen would discover X-rays a little over 50 years later. His premise was like those before him "*sounding of the bladder alone often misleads*. *It appears therefore more successful that the sense of hearing should help the sense of touch*." He worked on cadavers and noted "*For this I connected usual sounding tubes with an ear trumpet and named these two parts the lithoscope*" [30]. Pfriem's lithoscope consisted of an ear trumpet made of hard wood resembling a goblet or wine glass and described as parabolic. This served to amplify the sounds from contact with a bladder stone. The attachment piece was another inverted bell-shaped opening for the insertion of the various probes or sounds. His Figure 6 shows three different types of curved probes (Fig. 20.3b). Probe A was made longer and of solid steel that could be manipulated and fixed to the acoustical device with a screw. Probe B was a hollow brass tube provided with some drainage holes. Probe D was again a solid steel smaller version for pediatrics. There apparently was a clinical trial in two patients, an infant aged 20 months and an adult aged 39 [31]. The young physician was timid with his new device, he stated "*Only by constant practice can this technique be better that the conventional sounding*. *The physician and the patient have to be willing to perform repeated examinations*, *in different body postures*, *with full and empty bladder*, *including the use of different modes of probes and their specific sound effects*" [31].

Let's briefly return to Sir Henry Thompson and his career as one of the first urologists and recognized leader of bladder stone surgery at least in England. His popularity and renown cannot be overemphasized. It is not clear how he first developed his interests in lithotomy or lithotripsy, but from an early age he was exposed to surgical instruments and surgeons. When he was sick, his physician was Dr. Jeaffreson who practiced in Framlingham and showed him a Civiale lithotrite. It is also known that the famous French lithotritist Baron Heurteloup visited the same town to perform a lithotrity on Mr. Jasper Pierson. It is known that following his surgical training in London, he traveled to Paris to work with Civiale himself in 1847. His first major case was when he was called in to perform lithotrity on King Leopold of Belgium after both Civiale and Langenbeck had failed. This was on June 6, 1863. He was also called as noted earlier to aid Napoleon III in January of 1873 where he failed. This certainly contributed to his development of an electronic microphone-enhanced sound to better evaluated bladder stones (Fig. 20.3c) [32].

Stones and Early X-rays

John Macintyre in Edinburgh published his historical paper of the first clinical use of the new X-rays in a patient with stone disease on July 11, 1896 [33]. Macintyre began, "*During the past 4 months I have*, *at the request of several physicians and surgeons*, *tried to photograph some cases in which the presence of renal calculus was suggested by the symptoms present*." He reported that he at first tried to X-ray and photograph prepared stone specimens ex vivo. This already had been done, however, by April 21, 1896; Félix Guyon presented a radiological appearance of urinary and biliary stones ex vivo [34]. Macintyre then went into the clinical details; he had been asked to X-ray a patient of Dr. James Adams of Glasgow who had already had a stone with surgery and was again symptomatic. He apparently noticed a recurrent stone on his X-ray photograph after 12 min of exposure time. The surgeon confirmed the location and size of the recurrent calculus, and a new era had dawned.

Swain followed Macintyre and published a case of a patient with a calcium oxalate stone made by X-ray that measured 1 1/8 × 7/8 × 5/8 in. [35]. He predicted the rise of radiologic diagnosis in the management of stone disease. He also evaluated stones ex vivo and included biliary calculi. He called the ability to visualize a stone "irradiability" and created a table to demonstrate X-rays abilities to image a stone:

Specific gravity	Permeability to X-ray	Density of shadow
Calcium oxalate	Biliary calculi	Calcium oxalate
Uric acid	Uric acid	Phosphates
Phosphates	Phosphates	Uric acid
Biliary calculi	Calcium oxalate	Biliary calculi

One of the first textbooks on X-rays was Henry Snowden Ward's 1896 work entitled *Practical Radiography* [36]. An American book followed a bit later in the year by an electrical engineer, Edwin Hammer, and a New York City physician, Henry Morton (*X-Ray; or, Photography of the Invisible and its Value in Surgery*). In their work, Morton and Hammer speculated rather presciently about many of the future applications regarding the new ray [37]. Morton would continue in the field and published *The Archives of the Roentgen Ray* beginning in July of 1897. David Walsh published the first medical textbook in1897, *The Röntgen Rays in Medical Work*. He covered a large possible scope for application. Francis Williams from Boston published his 1902 textbook called *The Roentgen Rays in Medicine and Surgery*. Here he describes the possibility of diagnosing stone disease. In 1908 Mihran Kassabian of Philadelphia published his *Radiography, X-ray Therapeutics and Radium Therapy* where he also mentions genitourinary applications [34]. This brings us to E. Hurry Fenwick's 1908 textbook *The Value of Radiography in the Diagnosis and Treatment of Urinary Stone. A Study in Clinical and Operative Surgery* [38]. "*Two groups of professional workers are mainly concerned in a careful study of shadows cast by the Röntgen rays in the urinary tract-the operator and the radiographer. Both work independently and yet both are interdependent. The former cannot justly cast the responsibility of shadow deduction upon the latter, though he is dependent upon him for skill in shadow detection. The radiographer cannot be content with merely producing shadows: he must aspire to the knowledge of their causation, and to obtain this he must examine critically and learn from the work of the operator. Each must give: each take*" [38]. There is no better opening paragraph to a new era of diagnosis than this one. Fenwick delineated the course of the ureters trying to limit the risks of phleboliths (calcified venous valves in the pelvis) which had caused false-negative ureteral explorations. His book has 11 chapters and is richly illustrated by 80 X-ray plates (Fig. 20.2b). At this early phase of radiography, this textbook is amazing and clearly points out the potential for changing the way stone patients are diagnosed.

A. Béclère followed the pathway set earlier by Swain and calculated the atomic weights of the elements that make up stones and also correlated this with the X-ray ability to visualize the stones [39]. He noted that of the various salts such as carbonates, urates, and oxalates, the absorption of X-ray increases with the atomic weight of the salt. In order of their increasing capacity of absorption, he listed the stones as follows: urate of ammonia, sodium urate, magnesium urate, potassium urate, and calcium urate. These were the greatest atomic weight salts, but he realized that the number of atoms and the molecular structure might also play a role in X-ray absorption. He realized that the majority of calculi that cast no shadows on X-rays were largely of uric acid. Calcium oxalate, phosphate stones, and calcium carbonate all were readily imaged. Cystine stones he noted cast a faint shadow. He even looked at rare xanthine and cholesterol stones and proved that they were akin to uric acid and were not at all imaged. He noted "*The X-ray never lies; it simply penetrates bodies in inverse proportion to their atomic weights-it is not the X-ray that is at fault, it is our interpretation that is at fault*" [39].

The urology groups at Johns Hopkins and New York Hospital followed as well. O.S. Lowsley noted that the most common causes for X-ray to fail in the diagnosis of stones are the following [40]:

1. Faulty X-ray technique
2. Motion or breathing by the patient
3. Presence of gas in the intestines

4. Overlapping the calculus over bone shadows
5. Obesity of the patient
6. Failure to make a complete cystoscopic examination with retrograde pyelogram
7. Inexpert interpretation of the plates

Harvey W. Cushing (1869–1939), who is considered the father of neurosurgery and a gifted writer, won a Pulitzer Prize for his 1926 biography of his mentor and idol Sir William Osler [41]. Cushing was born in 1869, the tenth child from a family with strong lineage of physicians and scholars. He had just completed his internship at the Massachusetts General Hospital in 1895 when Röntgen discovered the X-ray. Cushing helped develop the early X-ray program in Boston. On February 15, 1886, a mere 6 weeks of Röntgen's report, Cushing wrote to his mother "*Every one is very excited over the new photographic discovery. Professor Roentgen may have discovered something with his cathode rays that may revolutionize medical diagnosis*." He and the house staff at MGH purchased their own X-ray machine, and when he left Johns Hopkins, it was rumored that he took the tube with him [42]. He certainly brought his radiographic interests with him to Baltimore, and he helped junior house staff develop the first X-ray equipment at Johns Hopkins. Let us relate the first X-ray examination performed at Johns Hopkins in Cushing's own words: "*It was in the fall of 1896 that I went to Johns Hopkins and made the first roentgenograms that were taken there, with the aid of a decrepit and perverse static machine as big as a hurdy-gurdy and operated in the same way, by turning a crank. My first paper submitted for publication contained an account of a case of a gunshot wound of the spine with plates showing a bullet which a Baltimorean had planted in the body of his wife's sixth cervical vertebrae*" [43]. He apparently became the technician during the early years, despite his grueling schedule as a resident of William S. Halsted's surgical service [44]. Another Hopkins' man who also interacted closely with Cushing was Hugh Hampton Young. We will discuss him later in some detail, but for the present, Young was given the role to develop genitourinary surgery by the chief, William S. Halsted. Hugh Hampton Young's textbook of Urological Roentgenology appeared in 1928. Now radiology assumed its modern foundation in the diagnosis and management of stone disease [45].

Let There Be Light

X-rays are not the only method to identify, quantify, enumerate, and locate stones. Light allows the physician to peer into the interstices of body cavities, with organs and organ systems [46]. The development of light-guided devices underscores the history and development of modern stone therapy [47]. At the dawn of the twentieth century, one early investigator of urologic applications who is better known as the "father of gynecology," Howard A. Kelly, demonstrated the potential of endoscopic evaluation of the urinary tract. Kelly and Curtis F. Burnam from Johns Hopkins published *Diseases of the Kidneys, Ureters and Bladder* in 1914 [48]. On page 270 of his classic textbook, Kelly noted that "*It is our habit in catheterizing ureters in practically all cases to wax the catheter tip before its introduction*." This was the era prior to X-rays; there were no fluoroscopes and only the hopes for illuminated endoscopes. Yet the need for knowledge about what pathology lies within visceral structures existed, and the ability of physicians to anticipate pathology grew as autopsies (the word *autopsy* means personal observation) increased in numbers and were correlated to clinical symptoms. The scratches on the freshly waxed catheters were critical to identify the presence and location of a potential ureteral calculus before other imaging strategies existed. Taking this one step further, Kelly also tried to remove the kidneys, bladder, and ureters transvaginally in his patients *postmortem*, in order to better understand their terminal illnesses [49]. The desire to investigate organs inflicted with pathology preceded the ability to actually do so. Next, a fringe idea was developed to actually inspect the organ or organ system. Typically, the individual(s) involved were not treated kindly by their peers. The rogue technique was found faulty, typically called cavalier or dangerous as we've seen in

Professor Kern's opposition to Jean Civiale's new technique of lithotripsy [50]. Finally, gradual improvement of the technical systems wins converts, and application becomes the norm. F. Mosteller wrote about the gradual introduction of technology in his classic treatise in 1980. New technology has an apparent life cycle with five stages: (1) feasibility (technical performance, applicability, safety complications, morbidity, mortality), (2) efficacy (benefit for the patient demonstrated in centers of excellence), (3) effectiveness (benefit for the patient under normal conditions, reproducible with widespread application), (4) costs (benefit in terms of cost effectiveness), and (5) gold standard [51].

A quick overview here in the introduction is followed by a more detailed historical development. The word endoscopy is derived from Greek meaning "to examine within." The first lighted examinations were external openings to the gastroenteral tract and the female introitus. Hippocrates' treatise on fistulas clearly mentions this technique, and later, Galen's *Levicom* refers to the catopter which is an anal speculum. Early Roman specula have been unearthed that record the foundations of primitive endoscopy. Early practitioners of medicine realized that to view a viscus from the inside should provide valuable information in the management of illnesses [52]. Philipp Bozzini (Germany) in 1805 constructed an instrument called "lichtleiter" for the viewing of the openings in the human body [53]. Bozzini's insight into the potential for direct visualization of the body is as amazing as the harsh criticism of his peers regarding his endoscopic adventures utilizing his device. Bozzini's light guide consisted of a housing in which a candle was placed. Open tubes of various sizes and configurations could be placed on one side [54]. He then devised a reflecting mirror between the visual tract and the candle light, so that the light would be reflected only toward the targeted organ and not backwards into the examiner's eye. The opposite side of the system was the eyepiece. He had published his results in 1806 and began to lecture in 1807 and even tried to have prospective studies of the instrument performed in military hospitals of the time (Bozzini). This development was remarkable in that it was the first use of reflected light as an illumination source. Unfortunately he was censured for his ingenuity since the intended use of the instrument was considered an unnatural act under contemporary mores. Bozzini died at the age of 35 after contracting typhus probably contracted during house calls [54].

Pierre Segalas (France) also reported upon the use of candles and a cone-shaped silver tube to reflect light into the urinary bladder. His refined urethroscope in 1826 which was primarily used in female patients was called "urethro-cystique" [55]. John Fischer from Boston also developed a functional but cumbersome elongated and angled speculum [56]. Anton J. Desormeaux (France) presented the first serviceable endoscope to the Academy of Paris in 1853. The light source for this instrument consisted of a reflected lamp fueled with a mixture of alcohol and turpentine, with which he performed numerous investigations of the urethra and bladder [57]. He was the first to identify that lenses serve to condense the light source beam to a narrower brighter region that allows for more intricate observations [58]. Bevan in 1868 utilized such a device to remove foreign bodies in the esophagus using a ¾-inch-diameter, 4-in.-length tube with a reflecting mirror [59]. Waldenburg in 1870 lengthened these instruments and referred to them as "telescopes." In 1881, American entrepreneur William Wheeler developed a "light pipe" which he hoped to deliver light to every household, but the incandescent bulb would become his chief rival [47].

Daniel Colladon demonstrated light guiding at the University of Geneva in 1841 [60]. Total internal reflection of light was made for a spectacular demonstration, and this mechanism was quickly artificially simulated by fellow physicist, Auguste de la Rive, using an electric arc light [47]. Jacques Babinet also took the method to use bent glass rods to examine difficult regions of the oral cavity in 1840 [3]. The Paris Opera began to use the same methods for spectacular stage effects in 1849 "*Elias et Mysis*" and again in 1853 for Gounod's *Faust* [47]. The International Health Exhibition held in South Kensington of 1884 displayed a giant "illuminated fountain" created by Sir Francis Bolton [47]. Other external illumination sources followed; however, the next major innovation was to be the development of an independent light source that could be transported into the body cavity being inspected. Julius Bruck (Poland) in 1860 examined the mouth using illumination provided by a platinum wire loop heated by an electric current within a water jacket [61]. This was the first galvanic endoscope and preceded the invention of Edison's filament globe by 20 years. There were numerous other descriptions throughout the remainder of the late nineteenth century on open-tube endoscopy procedures including Kussmaul's description of removal of a foreign body from the esophagus using reflected sunlight. Stoerk in 1887 designed a right-angled endoscope to allow greater manipulation away from the ocular [12]. In that same year, Charles Vernon Boys developed a method of creating small stretched almost pure silica fibers that could transmit light [62]. Rosenheim in 1895 employed a flexible rubber obturator for safer introduction and easier handling of endoscopes [63]. Kelling in 1897 designed a true flexible scope with small interdigitating metal rings covered by rubber on the outside [64].

Killian in 1898 first used cocaine anesthesia during bronchoscopy [65]. Nitze in 1879 pioneered the first modern endoscope for cystoscopy [66]. He worked with an optician (Beneche), an instrument maker (Leiter), and a dentist (Lesky) to create a 7 mm. deviating prismed endoscope with a liquid cooled glowing wire of platinum [67]. He followed this later with a separate light source, a miniature electric globe [68]. Maximilian Nitze was a general practitioner who thought that if an instrument could be introduced with ease, minimal pain, and relative safety, the endoscopes must be smaller [69]. His idea was to place lenses into the tubes at prescribed distances to focus the image at an ocular. In addition, his early version used a platinum wire in a glass jacket with water cooling methods. He began clinical investigations with this cystoscope in 1877. By 1879, Nitze's design team was aware of Edison's invention of the filament globe, and they immediately miniaturized it to fit into the tip of the cystoscopes. The first actual use of the Edison incandescent lamp for cystoscopic application was by Newman (Glasgow, 1883), followed by Nitze (1887), Leiter (1887), and Dittel (1887) [70].

In the United States, Otis designed a new cystoscope with telescopic lenses and a distal electric globe. The instrument maker for this scope was Reinhold Wappler (1900) and clearly became the premier optical system of that time. In 1936 Schindler worked with Wolf (an optical physicist) to design the first working flexible endoscope with steel spiral construction and 48 lenses [67]. As early as 1893, Albert Musehold described an apparatus to photograph the endoscopic appearance of the pharynx [71]. Nitze published the first photographic atlas of the pathology of the urinary bladder in 1893 [72]. On December 30, 1926, Clarence Weston Hansell, an RCA engineer, wanted to view images from a distance using fiber-optic bundles [73]. Henning and Keihack published the first color photographic pictures of the stomach in 1938 [74]. Rudolf Schindler developed a rigid, then a semirigid gastroscope, and Heinrich Lamm tried to reproduce Hansell's findings with fiber optics as a third-year medical student using commercially available optical fiber [47]. Lejeune produced the first motion pictures of the larynx in 1936 [47].

Abraham Cornelius Sebastian van Heel noted that cladding improved the light transfer and image quality of fiber optics and speculated that it could be used for cystoscopy in a letter he published in *Nature* [75]. Harold Horace Hopkins also published in the same volume of *Nature* with a young graduate student named Narinder S. Kapany, but their fibers were unclad [76]. Basil Hirschowitz (a physician) and Lawrence E. Curtiss (a physics student, later transferring to the American Cystoscope Makers, Inc.) working at the University of Michigan produced a fiber-optic gastroscope which was first tried on Hirschowitz and then presented at the annual meeting of the Optical Society of America in October 1956 in Lake Placid (site of the first digital televised sporting event using fiber optics) [77]. Numerous modern advances have contributed to our modern arsenal of endoscopic equipment (fiber-optic bundles, superheated halide element light sources, electronic charged-coupled devices, CCD, and others) [78, 79]. The need to be able to visualize and eventually operate with tiny endoscopic manipulators has revolutionized the management of stone patients. Now the technology existed to begin to explore the upper urinary tract. Advanced ureteropyeloscopic surgery is based entirely upon those pioneers' efforts from long ago that strived to better visualize the vital structures of patients suffering with assundried maladies without opening them [80, 81]. The ureters were always present and simply awaited pioneer endoscopists to explore the limits of technology.

It has now been over a decade since Perez-Castro Ellendt and Martinez-Pineiro first developed a designated rigid ureterorenoscope, almost three decades since Marshall visualized a ureteral calculus with a fiber-optic-bundled catheter, and almost 6½ decades since H. H. Young and R. McKay (1929) stumbled into the ureter in a child with posterior urethral valves [82]. They reported passing a 9.5-Fr pediatric cystoscope directly up to the renal pelvis of a child. Nearly 50 years later, Tobias Goodman not only passed an 11-Fr pediatric cystoscope into the ureters, he also became the first to perform interventional surgery to the upper tracts by fulgurating a low-grade transitional cell carcinoma of the ureter [83]. One year later Lyon dilated the distal ureter to 16 Fr with Jewett sounds to perform ureteroscopy with a 14-Fr resectoscope [84]. This same group first deployed the first purposely built ureteroscopes (13 Fr) for examining the distal ureter [85].

In 1980, Perez-Castro Ellendt and Martinez-Pineiro developed the longer scopes that have allowed visualization to the entire urinary tract, nephroureteroscopy [86]. The first fiber-optic endoscope was developed for the use in gastroenterology by Hirschowitz as previously described in 1957 [77]. Victor Marshall placed a fiberscope antegrade during an open exploration to visualize the pelvis and distal ureter in 1960 [87]. It did not take long for Marshall's colleagues to decrease the size of these fiberscopes, and McGovern and Walzak utilized a passive fiber-optic scope transurethrally in the urinary tract in 1962 [87]. Takagi utilized such a scope to visualize the caliceal anatomy in humans in 1968 [88, 89]. Takayasu and colleagues developed and utilized a flexible ureteropyeloscope clinically by 1971 [90].

Throughout this time, urologists have managed to extend the limits of visualized access to the recesses of the urinary tracts. There have been improvements in optical imaging systems, both rod lens and fiber optic. Illumination systems provide unprecedented color and brightness secondary to halide lamps. Minimization of the trauma of access is the result of smaller and smaller ureterorenoscopes. Finally, by moving the surgeon's eye away from the ocular, video camera systems allow the urologist the freedom to control complex endoscopic interventions. Electronics is now the key to many of these newer innovations. The charged-coupled device was invented by George Smith and Willard Boyle at the Bell Laboratory on October 17, 1969, for electronic video recording. This was rapidly applied to fiber-optic technology initially by Welch Allyn in 1983. Japanese makers Olympus, Fuji, and Pentax all introduced video endoscopy in the early 1980s [91]. Equipment for manipulating ureteral and renal pathology has kept pace with the development of smaller and smaller endoscopes including all of the accoutrements now typically associated with ureteroscopy: guidewires, access sheaths, stents, and baskets [92–102]. The only real question is how small is enough and can high-quality operative instruments allow the endoscopic surgeon to perform necessary interventions in every portion of the urinary tract?

Finally, the limit of imaging probably depends upon stability of the shaft, the ability of an ocular eyepiece to magnify and focus microscopic fiber bundle transmissions, and the ability to simultaneously irrigate and work. Michael Marberger estimates that this limit is approximately 4.8 Fr. This was originally proposed at the World Endourology Congress in Singapore in 1992 [103]. Regardless of costs, urologists throughout this country and the world are seeking ever-improved methods of dealing with upper tract pathology in a cost-effective, minimally invasive, nonhospital setting [104]. Perhaps robotics and automated microdevices or even autoilluminated human urine can serve as an in vivo imaging systems [105]. Alexander Pope once stated, "Be not the first by whom the new are tried, Nor yet the last to lay the old aside" [106].

Modern Radiologic Diagnosis

It is apparent that almost immediately following the discovery of X-rays, the number of clinical applications rapidly rose in medicine. The 1920s were the boom years for radiology, the newly appointed division of medicine that dealt with use of X-rays [107]. There was a period when the X-ray was exploited for showmanship, but it was rapidly recognized that there were substantial harmful effects of the ionizing radiation.

The rise of X-ray utilization has become so prevalent that the frequency of examinations in the USA is estimated to be one per capita [108]. In the 1930s and 1940s, mass screenings using X-rays were employed to identify patients with tuberculosis. In the 1960s mammography developed for screenings of breast cancer. In the 1970s computerized tomography was on the rise and has rapidly become the gold standard for patients with stone disease. It has been estimated that a CT scan has about 8 milliGray or about 200× the dose of an ordinary X-ray. In the 1990s about 9 % of all X-rays in the USA were now CT scans. The number of radiologists has expanded faster than the population of the USA! [108].

At the Hôpital Necker in Paris, the department of urology was strongly interested in stone disease, and Félix Guyon helped promote the first X-rays of stones. By 1897, the first four radiological laboratories had been created in Paris, and by Guyon's colleagues Théodore Tuffier and Janet introduced the ureteral catheters and X-rayed the patients. Joaquin Albarran (1860–1912) was a Cuban-born urologist trained in Barcelona but had come to work with Guyon. He developed a whole host of technologies to improve the radiologic diagnosis, including the first radiolucent catheters. Albarran was the first urologist to ever be nominated for a Nobel Prize in 1912, but he died just prior to the election [34]. Howard Kelly worked with finely waxed catheters prior to radiology that would become scratched or etched when encountering a stone [49]. The X-ray was a vast improvement over this nonspecific methodology. By 1914, another urologist named Pasteau developed a marked semiopaque centimeter-scaled ureteral catheter. Contrast materials were thought of; the first utilized were air, oxygen, and carbon dioxide. In 1903 Wittek injected air into the bladder to better X-ray and identified a bladder stone. In 1905 Wulff and Albers-Schönberg in Hamburg injected air and bismuth into the bladder of a stone patient [108].

Then in 1906 the German urologists Voelcker, von Lichtenberg, and Czerny began to investigate opacification agents with a variety of compounds including bismuth, lithium, silver, and then thorium. By 1914, Albarran began to use their silver compound (Collargol®) to perform retrograde pyelograms. Marcel Guerbet, a French chemist, had suggested using nontoxic iodinated compounds to Albarran. A German compound Iodipin® from Merck Darmstadt was followed by Lipiodol®. Sodium iodine was used at the Mayo Clinic in 1923 by the pharmacist Rowntree to visualize the bladder on a syphilitic patient. Osborne and colleagues followed with a clinical trial with no great success, but Graham and Cole switched to iodinated phenolphthalein in 1924 [109]. Thorotrast® was a sodium iodine solution for intravascular X-ray exams, but it was found to be carcinogenic. Legueu and colleagues utilized it in the 1920s for retrograde urography. In Berlin between 1928 and 1929, the synthesis of a water-soluble iodinated contrast agent was undertaken by a young American urologist, Moses Swick, who worked for Alexander von Lichtenberg. He was in Leopold Lichtwitz's clinic at the time and knew that Binz and Rath had synthesized a new benzoic acid iodinated material. He tried this new compound, Selectan Neutral®, on rabbits and obtained intravenous pyelograms. Swick took the new material and tried it on humans [110]. Von Lichtenberg began the official study using Uroselectan®, and the IVP became the mainstay for diagnosing urolithiasis [111].

Ultrasonography currently is utilized extensively in Europe for following patients with stones. The examination is simple and can be repeated without irradiation. All patients with stones, from children to pregnant women, do not detract from its usefulness. Ultrasonography loses its specificity in following ureteral stones and correctly predicting the degree of obstruction. Ultrasonography cannot discriminate between radiopaque and radiolucent stones. The quality of the examination has been shown to be user dependent with a sensitivity of 93 %, positive predictive value of 93 %, specificity of 83 %, and a negative predictive value of 83 % [112]. Ultrasonography is maybe readily available at many institutions on an emergency basis, and the decreased reliability and lack of physiologic information have relegated its primary utility to following stones in pregnancy and children in the USA.

The intravenous pyelogram (IVP) was the "gold standard" evaluation despite recent detractors favoring other methods. After the development of Uroselectan®, Schering AG developed Uroselectan B® and then Diodone®. Bayer came out with Abrody®, and the French developed a deiodinated molecule called Tenebryl®. By 1930, Coliez noted that improved imaging was possible with ureteral dilation, and Zeigler developed an abdominal compression device to aid upper tract visualization. Von Lichtenberg summarized all of these developments in 1931 [113]. IVP provides accurate size, shape, location, and functional data regarding the calculus and the kidney. In one recent evaluation, the IVP revealed unexpected findings in 42 % of patients and altered the management strategy in 60 % [114]. The primary limiting factor in modern centers is the ready availability of the superior imaging modality, CT scanning.

Non-contrast helical CT scanning represents the new "gold standard" for the emergency evaluation of colic. J. Ambrose and G.N. Hounsfield presented some preliminary data at the April 1972 Annual Congress of the British Institute of Radiology on a new computerized tomographic imaging system for the brain [115]. Hounsfield followed this up with the first published CT images in 1973 [116]. CT scanning has since massively proliferated. In March of 1984, the group from the Massachusetts General Hospital looked at 35 excised kidney stones to establish CT density characteristics for stones. This was the first significant study to evaluate the possibility of using CT not only to diagnose the presence of a stone, but also to see if the CT had the comparative ability to differentiate the composition of the stone. The problem of course is that the stones were ex vivo, and the findings did show that both cysteine and uric acid stone types could be accurately identified [117]. By 1998 CT scanning for acute colic had essentially become the gold standard for diagnosis [118].

The signs of obstruction on such scans include the following: stranding of perinephric fat, dilated collecting system, dilated ureter, and stone localization [119]. Proponents for these studies have helical CT scanners available to their emergency departments at all times. In addition, they quote the faster scan times (2–5 min. for CT) versus IVP (5 min. to >5 h). The sensitivity for the helical CT scans has been reported at 95 % with a specificity of 98 % and a diagnostic accuracy of 97 %. Additionally, these authors have diagnosed unrelated pathology including adnexal masses, appendicitis, diverticulitis, pyelonephritis, common bile duct stones, and others [119].

Lastly there exists another modality to investigate functional renal obstruction that can add immensely to the management of patients with acute renal colic—radioisotope renal scanning. Renal scanning can be used when patients are allergic to intravenous contrast. It provides information on renal function, morphology, and blood flow [120]. Diuretic isotope renal scanning may add further to the sensitivity and specificity of the diagnosis of acute renal obstruction caused by stones [121]. The primary detractor for diuretic radionuclide scanning is the lack of diagnostic accuracy. Obstruction can be demonstrated as well as reduced function, but the etiologic cause cannot be determined.

Other modalities are evolving for assessing ureteral obstruction. Magnetic resonance urography has been described, and duplex ultrasound systems can calculate resistive index to correlate with the severity of obstruction. Yet a urinalysis revealing hematuria combined with a plain abdominal radiograph (KUB—for kidney, ureter, bladder) has a 95 % sensitivity and 65 % specificity with 82 % positive predictive value and 88 % negative predictive value [112]. The utilization of US, IVP, non-contrast helical CT, and radionuclide diuretic renal scans can add information in patients whose clinical scenario is complex or not responding to standard measures. Which test is most appropriate depends upon your own setting and the availability of specific imaging modalities with the associated qualified staff to interpret them.

Conclusions

The evolution of imaging to identify the elusive urinary tract stone has been the focus of this chapter. We have used metaphors from Faulkner and Paul Simon to introduce problems that past physicians encountered when attempting to make the diagnosis of urolithiasis. One further musical metaphor can summarize the pre-X-ray and endoscopic era; it was akin to "*Dancing in the Dark*." This is of course the title of the "*The Boss*," Bruce Springsteen's 1984 hit single that was also the final piece recorded for his number one album, *Born in the U.S.A* [122]. The song was written following an argument with Springsteen's producer John Landau, and the intent was to show the frustration that he must have been feeling to finish the album. This is similar in a lyrical sense to the lithotomists or lithotripter not knowing if there was a stone present or not or if the stone was simply too big to be done via the perineal route or by a lithotrite. But the ultimate harmonic parable for the mystery of stone disease, the horrors of surgery, would be the music of the French composer, Marin Marais (1656–1728). The *Le tableau de l'operation de la traille* describes the surrealism of stone disease and the agony of stone surgery. Marais was both a composer and a gifted performer on the bass viol which comes the closest to the human voice [123]. It is not known if Marais suffered from stones, or even underwent the surgery for a stone, but his musical piece certainly suggests an intimate association with the horrors of this experience, even as far as sounding for the stone.

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21 Rise of "Science" in Stone Disease

Introduction

> "*How much has happened in these past 50 years- a period more remarkable than any, I will continue to say, in the annals of mankind. I am not thinking of the rise and fall of Empires, the change of dynasties, the establishment of governments. I am thinking of those revolutions of science which have had much more effect than any political causes, which have changed the position and prospects of mankind more than all the conquests and the codes, and all the legislators that ever lived.*"
>
> —Benjamin Disraeli, 1873 [1]

The Enlightenment ended with the development of the appreciation of mankind's abilities to advance and understand nature but did not have the tools to pursue the quest that knowledge offered. Bacon enshrined the notion of applied knowledge in the pursuit of perfection, but it was glimmer of possibility. Bacon also suffered from gout and bladder stones. He might have consulted with William Harvey who apparently did not like the Lord Chancellor [2]. Following in the footsteps of Francis Bacon at Cambridge University were four gifted polymaths at Trinity College in the early nineteenth century. One of them, William Whewell, coined the term "scientist" and institutionalized its modern usage in our language's lexicon [3]. Poignantly his name is also linked to urolithiasis as well, because the most common type of stone, calcium oxalate monohydrate, enshrines his name, whewellite (mineral name) [4].

We began this textbook about the history of history itself, but failed to discuss the scientific ramifications of history. It would appear that modern science is little concerned with history, even history that specifically impacts the subject of the science, in this example, urolithiasis. If this were taken even further, there is almost a pronounced disdain for the topic of history, even though most thoughtful individuals would point out the necessity of documenting the past, though having no specific opinion upon its necessity. Isaac Newton could represent the epitome of the scientist; he was antisocial or perhaps even asocial [5]. He was arrogant, argumentative, viciously held a grudge, and vindictive. The only known portrait of his hated rival Robert Hooke which used to hang in the Royal Society has never been found since the reign of Newton as president of this organization. But Newton enshrined the concept of history in science in his comments to his nemesis, Hooke, regarding his groundbreaking paper on white light: "*What Des-Cartes did was a good step. You have added much several ways, and especially in taking ye colours of thin plates into philosophical consideration. If I have seen further it is by standing on ye shoulders of Giants*" [5]. Newton was perhaps both being derogatory to the hunched, small stature of Hooke as well as self-aggrandizing his own abilities. But he also took this metaphor from the twelfth-century cleric, Bernard of Chartres, who said "*nani gigantum humeris insidentes*" (like dwarfs [Hooke] standing on the shoulders of giants) [6].

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Science Itself and Stone Disease

Prior to the writings of Francis Bacon, one can see that the development of a method for the detailed investigation of nature was typically haphazard. Francis Bacon (1561–1626) was an attorney and civil servant but had an irrepressible intellect that strove to understand nature. He was dazzled by the ability of progress to change the future and wrote about his vision accordingly: "*Bove all, if a man could succeed , not in striking some particular invention, however useful, but in kindling the light in nature- a light which should in its very rising touch and illuminate all the border-regions that confine upon the circle of our knowledge; and so, spreading further and further should presently disclose and bring into sight all that is most hidden and secret in the world- that man (I thought) would be the benefactor indeed of the human race- the propagator of man's empire over the universe, the champion of liberty, the conqueror and subdue of necessities*" [7]. He laid the foundations for the rise of the Royal Society and the British Association for the Advancement of Science. Both would claim a legacy that began with Bacon.

William Whewell was born on May 24, 1793, to John and Elizabeth Whewell in Lancaster. John Whewell was a carpenter and wanted his eldest son to follow him into his trade. By all accounts, William was quite good at this and pretty much at everything he tried in fact. He breezed through school where he drew the attention of Reverend Joseph Rowley, the parish curate, and the Owens family, whose son Richard Owen would likewise make an academic career out his life. Reverend Rowley saw something special in William and convinced the father that an education would get young Whewell farther than the carpentry trade. He was brought along quickly and was accepted to Trinity College, Cambridge. He made many lifelong friends, got a second Wrangler in his Tripos, and won a scholarship. He was outstanding in both the classics and the sciences. He was an active member of the "Philosophical Breakfast Club" that admired the future as depicted from the fellow Trinity luminary, Sir Francis Bacon [3]. If "*knowledge was power*," Whewell saw himself and his friends as the official vehicle to bring about Bacon's method to science and the application of new ideas for the benefit of mankind. After graduation Whewell stayed at Cambridge to study for the fellows examination, and he joined the Cambridge Union Society, a debating group. After winning his Fellowship he began to study minerals and experiment on crystals. Whewell became the professor of mineralogy in 1827 till 1832 after becoming an Anglican clergyman. In 1830 Herschel's *Preliminary Discourse on the Study of Natural Philosophy* was released that introduced the Bacon's method in broad terms [8]. This was followed by Charles Lyell's first volume of *Principles of Geology* in the same year [9]. Whewell wrote about both coining the terms "uniformitarianism" for Lyell's view of geologic history and "catastrophists" for those who apposed these ideas. Whewell became the person whom the next generation would turn to for names of new discoveries. The development of the British Association for the Advancement of Science by Vernon Harcourt served as a vehicle for advancing Bacon's notions, as well as providing another arena for science other than the Royal Society [3]. Whewell did not attend the first meeting in York on September 6, 1831, but 353 participants were present and he strongly encouraged the new organization [3].

Whewell's interests were broad and general. He obviously was interested in mineralogy, crystals, and geology. He was interested in mechanics, architecture, physics, tides, astronomy, economics, electricity, poetry, literature (he translated works of Goethe), and theology [10]. His first major work was An Elementary Treatise on Mechanics in 1819 [11]. He hosted the 3rd Annual Meeting of the British Association for the Advancement of Science in Cambridge in 1833, and he became the Master of Trinity College, Cambridge, in 1841. While the headmaster, notables such as Charles Darwin, James Clerk Maxwell, and William Thompson who together would represent the next generation of science all came under his profound influence. Both Maxwell and Darwin noted specific instances of Whewell's influence on their thinking. Darwin specifically mentions Whewell's Bridgewater Treatise in his 1859 *On the Origin Species by Means of Natural Selection*. Whewell's list of friends and correspondence is massive and became the unofficial neologist for the birth of nineteenth-century science especially advising Michael Faraday, coining the terms "*ion, dielectric, anode, cathode*" and a whole host of others including the word "*physics*" itself [3]. It is ironic that Whewell's liberal ideas of science were so prophetic during his lifetime, yet, he and most of those who were most profoundly influenced by his thoughts rose against Charles Darwin's revolutionary theory of evolution by natural selection. In fact, the Master of Trinity had *On the Origin Species by Means of Natural Selection* banned from the Trinity College Library which was an architectural wonder designed by Christopher Wren.

Disease Itself

Antonio Benivieni (1443–1502) wrote his *De Abditis Nonnulis ac Mirandis Morborum et Sanationmum Causis* (About the Hidden Causes of Disease) which included 111 cases and 20 postmortem examinations [12]. In his work *Medicina* which included one section called *Pathologiae Libri*, Jean Fernel (1497–1558) noted more types of organ-specific pathology [13]. Théophile Bonet (1620–1689) published his *Sepuchretum sive Anatomica Practica* in 1679 [14]. Giovanni Battista Morgagni (1666–1771) followed with his monumental *De Sedibus et Causis Morborum per Anatomen Indagatis* (About the Seats and Causes of Diseases Through Anatomical Investigation) in 1761. He describes the findings in over 640 autopsies. We have discussed his influential works and the description of autopsy findings of stone disease [15]. John Hunter (1728–1793) also dissected dead patients and sought to understand the pathology that made his attempts at crude surgery so ineffective in some diseases. Hunter's nephew was another talented investigator, Mathew Baillie (1761–1823) [16]. Baillie wrote a treatise in 1793 *The Morbid Anatomy of Some of the Most Important Parts of the Body*. Marie Francois Xavier Bichat (1771–1802) was born in the same year that Morgagni died. He became a gifted investigator and wrote several works in his very brief life [17]. He identified 21 types of tissues and began to use the microscope to chase disease: [18] "*Science requires, in our anatomical books, some general considerations like these, to precede the treatise of each organ system, such as the nervous, vascular, muscular, boy, ligamentary, and others; considerations, which form the most beautiful part of the study of the animal structure, and which exhibit nature every where uniform in her operations, varying only in their results, sparing of the means she employs, prodigal only in the effects she obtains; modifying in a thousand ways a few general principles which, differentially applied, preside over our economy, and constitute its numberless phenomena*" [19]. Gabriel Andral (1797–1876) followed in Bichat's wake and published his 1828 *Précis d'Anatomie Pathologique* [20]. Thomas Hodgkin (1798–1866) utilized the improved compound microscope of Lister (father of Joseph Lister) in his 1832 publication *Lectures on Pathologic Anatomy*. In this he noted "*Lister's compound microscope might lead to useful discoveries in the future*" [21]. Carl von Rokitansky (1804–1878) became a massive authority on disease and pathology. He performed Beethoven's autopsy as a young physician and noted carefully his kidney stones [22]. He also became the mentor of another young student who already drank deeply from the knowledge of human bodies as a student under Johannes Müller (1801–1858) from Berlin. This student would eclipse all them; his name was Rudolf Virchow (1821–1902) [23]. The great founding fathers of pathology did not significantly discuss much about stone disease, sadly and mostly were concerned about the bladder stones.

Let's look briefly at just Mathew Baillie's textbook of pathology (1761–1823) as an example. Baillie wrote a treatise in 1793 *The Morbid Anatomy of Some of the Most Important Parts of the Body* [16]. He began with the reasons for the significance of autopsy in better understanding disease: "*Another advantage arising from a more attentive observation of morbid structure is, that we shall be better fitted to detect disease alterations*

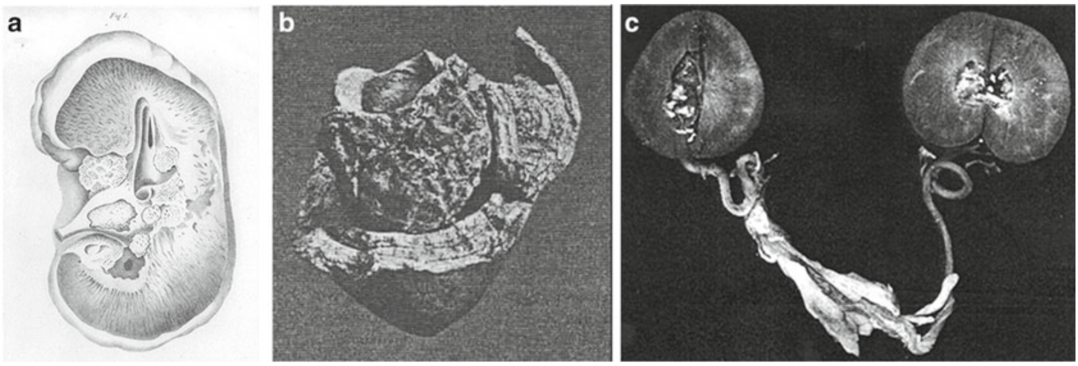

Fig. 21.1 The rise of science in stone disease. (**a**) John Green Crosse's Plate 6, Fig. 2. This demonstrates intrarenal stone formation and comes very close to depicting what are now called Randall's plaques. (**b**) Samuel G. Shattock's illustration of the young male predynastic Egyptian pelvis with bladder stone. (**c**) Wilhelm Ebstein's famous animal model of stone formation from 1896

in the organization of parts that are but little, or not at all known. This will lay the foundation of our inquiry into the diseases themselves, so that we shall add to our knowledge of the pathology of the body, and perhaps also to our knowledge of remedies" [16]. Baillie's chapter eight was his dissertation of diseases of the kidneys: "*The formation of calculi is not peculiar to the kidneys, but it is a more frequent disease in them than in any other part of the body. Small granules of stone are sometimes found in the tubular portion of the kidneys; but it is more common to find a calculus of considerable size lodged either in some part of substance of the kidney, or in the pelvis or the ureter*" [16]. He either has not looked closely at the papillary tips or the death of his patients from stones had not developed the papillary lesions that are so commonly associated with this disease nowadays.

John Green Crosse's morbid anatomy of stones was one of the early textbooks to discuss kidney stones and the potential for morbidity and mortality. Specifically highlighted here are extracts from his chapter four entitled *Chapter IV. Of Calculi in the Kidneys and Ureters, and Their Pathological Effects* [24]. He begins with the following statement: "*Several writers mention having found gravel or small crystals of lithic acid in the tubuli uriniferi of the kidney; considering the frequency of this form of urinary deposit, such a pathological state is rarely demonstrated; of the many dissections I have made, always taking care to inspect the kidneys, I have in not more than two or three instances found red gravel so situated*" [24]. Thus, he began a more enlightened investigation of the kidneys of stone formers. His first case, an autopsy of an elderly man who died of pyohydronephrosis and stones, shows a kidney with "*The parenchyma being cut through in different directions, the tubular part was found occupied by numerous white concretions, varying in size of the smallest sees to that of a large pin's head; these bodies were distributed over all parts of the substance of the kidney except the cortical portion; on more minute investigation, I found them to be pure oxalate of lime, crystallized, transparent, and situated in the tubuli uriniferi*" [24].

Crosse clearly was following the pathway already reported on by Hunter, Bichat, and Baillie but more significantly focused on urolithiasis. His illustrations of stones in the kidneys are curiously associated with, though not described by him in any chapter, papillary stones that appear to be fixed at the tips (Fig. 21.1a, **from Crosse's Plate 6**). He is perilously close to the findings of Randall almost 100 years later.

William Ord

William Miller Ord was born into a medical family; his father was a general medical practitioner in Streatham. William was his oldest son and attended King's College in London. He graduated with honors and obtained his M.B. in 1857. He also won the Cheselden Medal as a medical student and was elected as house surgeon at St. Thomas's. He left his station to aid his ailing father in practice and returned as a lecturer on zoology. His textbook called *Notes on Comparative Anatomy: a Syllabus of a Course of Lectures delivered at St. Thomas's Hospital* was his legacy to these early years [25]. He became a member of the Royal College of Physicians of London in 1869. He was subsequently elected by his colleagues to become the Dean of the Medical School [26]. By all accounts, Dr. Ord was a great bedside teacher assuming the duties of his predecessor Dr. Murchison. His output of activity was impressive and he held the reins with extensive clinical duties for 16 years. He relinquished the chair of medicine in 1894 but taught on the wards for another 4 years. He was an avowed bibliophile with wide-ranging interests in botany, geology, as well as comparative anatomy. Ord worked out the clinical ramification of an obscure "*Cretinoid Condition*" and coined the term myxedema and gave the Bradshaw Lecture in 1898 on this condition [27]. He also became interested in Neurotic Dystrophies and gave the address to the British Medical Association on this topic in Belfast 1884 [28]. Dr. Ord corresponded with Charles Darwin on various subjects.

William M. Ord was a medical physician, researcher, and teacher at St. Thomas's Hospital and the final pupil of George Rainey. He like Henry Vandyke Carter also continued his own personal researches on "molecular coalescence" and stone disease itself [29]. He wrote his influential work *On the Influence of Colloids upon Crystalline Form and Cohesion, with Observations on the Structure and Mode of Formation of Urinary and other Calculi* [30]. This book had nine chapters, the first two essentially reiterated his work with Rainey, his mentor. We are interested in the final seven chapters that move to clinical investigations on specific stone types. Chapters three and four started his work on purine stones, specifically uric acid and its salts. He reviewed all of the recent writings on uric acid including Prout, Carter, and Beale. He noted that different crystal types of uric acid form in response to changes in the urinary environment, especially the presence of albuminuria. He noted that patients with diabetes have glucose in their urine likewise effects crystal size and morphology. Finally he noted that albumin and sugar in the urine resulted in sheets of uric acid precipitation, whereas just sugar was associated with the more rhomboidal form. He repeated experiments on both sodium urate and ammonium acid urate and similarly notes phase changes in crystal moiety by amounts of colloid or sugar present [30].

In chapter five Ord moved to describe his experiments with calcium oxalate. He noted that in urine, there are three main crystal forms: the octahedron, the dumbbell, and occasionally small flat tabular forms. He believes that the dumbbell form is the crystalline form that precipitates to form calculi. He believes that simple addition of colloid to solutions of calcium oxalate can produce the dumbbell form and the increased risk of stone formation [30]. He concludes with the profound statement "*To mould oxalate of lime into calculi would seem to require denser colloids than are usually present in vesical urine, and it is probable that the beginnings of oxalic calculi take place in the recesses of the kidney among less diluted colloids*" [30]. He is correct in noting that these stones form only in the kidney but misses the location by not targeting the papillary tips, but this too will be resolved in time. He also published *An account of experiments on the influence of colloids upon crystalline form, and on movements observed in mixtures of colloids with crystalloids*. This is rather a summary of his experiments [31].

In the 1880s Ord began to publish a growing collaboration with his colleague in pathology, Samuel George Shattock, a series of investigations on stone disease from St. Thomas's Hospital and the Royal College of Surgeon's collections. In the Transactions of the Pathologic Society of London, the duo published a series of presentations on virtually every type of stone [32–34]. They continued to collaborate though each contributed individually to the literature as well. On the microscopic structure of urinary calculi of oxalate of lime appeared in 1895 and was an exhaustive summary on calcium oxalate stones [35]. Shattock followed with a series of detailed investigations as to the microscopic structure of uric acid and urate-containing stones. He detailed the crystallographic differences of uric acid and its varieties from the urates [36, 37]. This work will make him uniquely qualified to perform investigations on two very rare stones that would fall into his lap in 1901.

The Stones Speak

Samuel George Shattock was originally born Samuel Chapman Beatty on November 3, 1832. He attended University College and Medical School in London and probably fell under the influence of William M. Ord. He was always interested in pathologic investigations and won the Liston Gold Medal for research in 1873. He never practiced clinically and always favored doing pathologic studies and museum work. He is most famous for his 1900 paper on blood groups and was named by the Nobel Committee [38]. Shattock became the curator of Anatomy and Pathological Museum of the University of London in 1881. He was the professor of pathology at the University of London from 1884 to 1924. He lectured on bacteriology and gave the Morton Lecture on Cancer to the Royal College of Surgeons in 1893. He was the pathology curator for the Royal College of Surgeon from 1897 to 1924. He became a fellow of the Royal Society in 1917. Shattock also began investigations on the calculi catalogued at the Hunterian Museum (particularly mummies) and St. Thomas's Hospitals from 1880 onwards. He famously described the two oldest reported stones in humans in a 1905 paper entitled *An Egyptian Calculus. A prehistoric or predynastic Egyptian calculus* [39].

It is worthwhile and historically relevant to pursue this particular paper of Shattock's in some detail because for another seven decades, these stones would be the oldest known human stones ever reported. Shattock begins this paper with a discussion of the current hypotheses and facts regarding the origins of the primitive civilization rising around the Nile River Valley. He gives us the history of finding the remains of a 16-year-old boy by Professor G. Elliot Smith which he presented to the Museum of the Royal College of Surgeons in 1901 (Fig. 21.1b, **the pelvis and stone from Shattock's paper**): [39] "*The calculus was obtained under the following circumstances. In April, 1901, Professor G. Elliot Smith visited Upper Egypt in order to study the remains of the prehistoric people which were being excavated by Mr. David Randall MacIver and the late Mr. Anthony Wilkin*" [39]. He presents the sequence of events that procured this bladder stone: "*In one of the first graves dug out the donor observed the calculus lying amongst the pelvic bones. The grave was that of a boy, aged 16 years (numbered 2231 in Dr. MacIver's private notes). The tomb had been plundered at some ancient date, but a stone vase remained to show that the grave was that of an individual of the predynastic period- i.e. of the middle or later-middle prehistoric period, some generations at least before the advent of Menes, the first dynastic king (about 4800 B.C.)*" [39].

Now it gets good: "*After this brief historical introduction let me describe the calculus itself. About half of the white phosphatic crust enveloping it was broken off by the workman's pick, and its extreme friability subsequently led to extensive fracture in the process of transit, the harder "body" being as a result completely isolated*" [39]. He works on the stone very carefully because he also investigates whether this young lad also had bilharziasis (but no schistosomes or "*the chitinous capsule*" were found): "*As far as can be told by the readjustment of the fragments, the calculus had an extreme diameter of 6.5 cm. Its chief bulk consists of a white friable phosphatic crust averaging about 1.3 cm in thickness. The crust is distinctly laminated…and a distinct vertical or radial crystalline striation*" [39]. He goes on to analyze the various layers; the outer layer is mixed magnesium ammonium phosphate and ammonium urate with some calcium carbonate (infectious etiology implied) although endemic stones also can cause this combination in children. The nucleus is was cut, "*…in construction it wants the compactness and regularity of the latter; and, except at the periphery, it is honeycombed with spaces, the walls of which present a finely granular character*" [39]. So even in prehistoric times, the nucleus appears to have arisen from a separate process that led to accretion within the bladder. Finally, "*Similar crushings of the nucleus show coarsely columnar crystalline fragments like those of the body, and, in addition, compact groups of pale yellow crystals, clearly aggregations of uric acid like those which may be encountered in microscopic sections of uric acid calculi*" [39]. So our young male primordial Egyptian had initially uric acid stones.

There is a second case of an ancient Egyptian calculus embedded in the jewel of a paper: "*Since concluding the foregoing observations upon a predynastic vesical calculus, I have been enabled through the kindness of Professor Elliot Smith to examine a second calculus of somewhat later date. This calculus was found, together with three others, by Professor Elliot Smith in a grave in the II Dynastic period excavated at Naga-ed-dër (near Girga, Upper Egypt) by Dr. George A. Reisner on behalf of the Egyptological expedition…As they were found lying alongside the first lumbar vertebra, it may be assumed that they are renal*" [39]. This first ancient kidney stone is estimated only to be about 600 years later than the young male. Of the solo stone evaluated, it was 1.6 cm in diameter: "*The particular calculus sent to me…has the mamillated or tuberculated exterior suggestive of the mulberry variety of consistence. Here and there a deep yellowish-brown area occurs, but the coloration is due merely to staining, as the most superficial scraping at once brings into view the white powdery substance of the general surface*" [39]. Chemical analysis of this stone showed a mixture of calcium carbonate and calcium oxalate. He elaborates on his microscopic inspection of the crystals, "*The crystals I found to consist, not of octahedral, but the less common form of square prisms with pyramidal ends, or elongated tablets with parallel sides and obtusely pointed extremities*" [39]. Sadly, no gender or any other interesting forensic evidence is forthcoming.

Shattock had access to the Collections at St. Thomas' Hospital and the Royal College of Surgeons. John Hunter however was collecting stones from every source for upwards to three decades [40]: "*It is pleasing, nay, highly interesting, occasionally to descend from the height to which modern surgery has attained, and carefully retrace each step, until we arrive at the very base on which it rests, every stone of which may be said to be inscribed with the name of John Hunter; for not only did he supply the materials, and work them with his own hands; but, if proof were wanting of how much he left wherewith to adorn the superstructure, let us visit the far-famed Hunterian Museum, where we may take our stand, and exultingly exclaim, 'Si monumentum queras circumspice'*" [40]. Another physician with a pathological and investigational aptitude, Thomas Taylor, would perform the herculean task of writing up the findings of this massive collection, the Hunterian collection [41].

Mr. Taylor's investigations of these stones led to a rather peculiar generalization regarding the formation of stones as humans age. He believed that the nucleus of a renal calculus in infancy was predominately urate of ammonia and proposed to call them infantile calculus. The nucleus of young adults appeared to be predominately uric acid and in adults after their fortieth year of life had oxalate of lime at the nucleus [41]. These statements must have had some significant influence at this time for others would often quote his reference, without thought to others who had already written significantly including Marcet, Beale, Rainey, Bence Jones, and Vandyke Carter.

Physiology

Claude Bernard (1813–1878) was born in the village of Saint Julien and was educated in a Jesuit school and attended college in Lyon. Famously his first passion was a playwright, but he was persuaded to attend medical school and came to Paris [42]. After his internship at the Hotel Dieu but soon came to the attention of Francois Magendie. He became the preparateur for the Collège de France in 1841, and he married Francois Marie Martin (Franny) in 1845. By 1955 he succeeded Magendie as professor at the college, and he became the first chair of physiology at the Sorbonne. Napoleon III built Bernard a full experimental laboratory at the Muséum d'Histoire National. He believed that his claim to fame was simply that he brought the scientific method to medicine [43]. His findings came in waves, and he contributed to the understanding of the pancreas, the hepatic manufacture of glycogen, and the vasomotor system in 1851. In 1865 he wrote his famous discourse on scientific medicine called Introduction to Experimental Medicine [44]. Alexis Carrel said of Bernard "*Before him, medicine was purely empirical. He is responsible for the introduction of the scientific method in the art of healing*." Paul Bert wrote that "*In twenty years, Claude Bernard found more dominating facts, not only than the few French physiologists working beside him, but than all the physiologists in the world*." I. J. Henderson summed up Bernard's philosophy in one sentence "*His life was spent in putting questions to nature*" [43].

M. Morand first reported calcium oxalate stones spontaneously in the Black rat: [45] "*He [Morand] informs us that it is much more frequent in males than females; and that almost all Rats, when they become old, have stones in their urinary passages, and swellings and ulcers in the kidneys. In one Rat, M. Morand found twelve stones, of which nine had become the size of coriander seed, and three were smaller. From others he took out stones of the size of a grain of wheat. The composition of these stones was very different from that of stones found in other animals. Instead of having, like those, a somewhat spherical nucleus, serving as a basis to concretions which are formed round it in an infinite number of extremely thin layers, the present had the same composition throughout. Their shape was also different, some of them being oval, and others cubical: and the cubical ones, it is remarked, had always a shining surface*" [45]. The time was ripe to take animal models as the method for further elucidating the complexities of stone disease. Claude Bernard had shown physicians and physiologists the way.

Oskar Minkowski was born on January 13, 1858, in Alexotin, Russia (now Lithuania), at a bad time for Jews. His family hurriedly immigrated to Königsberg in Prussia. He attended medical school in Königsberg and fell under the spell of experimental research with his Professor Bernhard Naunyn whom he followed to the University of Strasburg where he worked until 1904. His major works were on the pancreas and diabetes; he was nominated for a Nobel Prize six times [46]. Minkowski developed an animal model to induce uric acid stone formation by large doses of adenine in dogs in 1898. He noted that the kidneys appeared inflamed after the administration of adenine to the dogs. He could not identify an increase in allantoin which was expected following a load of purines to these animals [47]. But it was a model for stone formation that others could follow and improve upon.

Wilhelm Ebstein (1836–1912) was a practicing physician, pathologist, chemist, basic scientist, teacher, and writer. He was born in Jauer (now Silesia, Poland) on November 27, 1836. He was influenced by the giants of his own era, Moritz Romberg, Emil Du Bois-Reymond, and Rudolf Virchow. He became a professor of medicine in Göttingen in 1874. Ebstein was prolific and published over 237 articles but we are interested in his work on stone disease [48]. He also was one of the first investigators to develop animal models for urolithiasis using various species. Arthur Nicolaier was his assistant in the laboratory. After feeding the animals, he specifically examined their kidneys (Fig. 21.1c, **one of the first animal models for stone investigation**). First, they investigated the use of adenine injected subcutaneously in rats to induce uric acid stone formation. They observed deposits within the kidneys [49]. Ebstein and Nicolaier similarly induce calcium oxalate crystals in the urine by feeding dogs large quantities of soluble oxalates in 1896 and 1897. He first noted calcium oxalate crystals in the renal tubules of animals as well as systemic toxicities such as muscle spasms and occasionally death [50]. Ebstein and Bendix obtained the same results in rabbits injecting adenine and observing the lagamorphs kidney for uric acid deoposition [51].

On October 1, 1900, an article appeared in the *Journal of Experimental Medicine* by the first woman (short of the quack section, i.e., Joanna Stevens) that we've mentioned in the history of urolithiasis, Helen Baldwin. This is fitting and ties in nicely with the history of urolithiasis as a woman will play a greater role in stone disease, and one of our final chapters is called Equal Rights. Helen Baldwin, M.D., came from a family of physicians, her father was Dr. Elijah Baldwin, and Helen was the fifth of seven children. She first started to practice in Philadelphia and then moved to New York City. She famously tried to help the black female physician, Harriet Rice, find a position. She was working in the laboratory of Christian Archibald Herter. Herter was a physician trained in experimental physiology by William H. Welch (later of Johns Hopkins fame) while he was at Bellevue in 1885. He served as faculty at several New York City medical schools and was instrumental in organizing the Rockefeller Institute for Medical Research.

Her paper on stone disease was entitled *An experimental study of oxaluria, with special reference to its fermentative origin* [52]. She began by stating her study was meant to follow up on Dunlop's notion that oxalic acid in the urine only comes from ingested sources and is not metabolized by an organism [53]. She noted "*Since the observations of Prout, it has been recognized that the oxalic acid taken in the food or in drugs may in part reappear unchanged in the urine*" [52]. She mentioned animal studies by Burggraeve (1862), Gaglio (1887), and Bunge (1889) that showed no rise in oxalates in dogs fed on meet alone. She reviewed all the pertinent literature on oxalic acid and dietary sources. She noted that spinach, rhubarb, dried figs, cocoa, tea, coffee, pepper, potatoes, beetroot, green beans, plums, tomatoes, and strawberries are rich sources of oxalate. She collected 24-h urine from 35 patients on random diets and measured the oxalate in the urine and correlated this with the presence of calcium oxalate crystals. She compared these urines with nine patients on a diet "free from oxalates" and then performed similar studies on dogs. She showed that the diets free of oxalates resulted in marked fall in urine values. She also noted that carbohydrates correlated with a rise in urine oxalic acid. She followed this with a dog study. She went on to perform a series of 11 experiments in dogs to determine if carbohydrates could form oxalic acid and the effect of varying doses of oral and parenteral ammonium oxalate on the kidneys [52]. She did succeed in producing acute oxalate nephropathy in some dogs, describing "*The most interesting lesion was in the kidney. Here the section showed numerous crystals blocking up the uriniferous tubules. Most of them were of irregularly shaped masses. Some showed characteristic dumbbell and ovoid shapes. These crystals were of a very light yellow color, were unstained by eosin or haemotoxylin, were insoluble in acetic acid and ammonia, but dissolved in dilute hydrochloric acid. There were no changes in the glomeruli. The cells lining the tubules were in places swollen and granular, and in places were torn away by passing of a calculus*" [52]. She credited Guinti from Milan in 1897 performing the first metabolic studies on oxalate absorption and metabolism. She concludes that oxalic acid is formed in living organisms and contributes to the renal load and that carbohydrate loading induces an increase in urinary excretion [52].

Yale University entered the battle against stone disease towards the end of the nineteenth century [54]. They carefully monitored the intravenous or intraperitoneal administration of several purine compounds adenine, guanine, and hypoxanthine and measured urine concentrations over time. Overall they noted that in the quadrupeds examined, uric acid was not the "chief end product" of purine metabolism. They then turned their attention to humans: "*Results obtained with animals seem can no longer be applied without reserve to man since the striking differences in the enzyme equipment of the different species has been pointed out*" [54]. They began a series of feeding humans ($n=2$ adult males, ages 28 and 25, weights 68 and 55 kg) various purine intermediaries and monitored for 20 days. They were given preparations with adenine, guanine, xanthine, and hypoxanthine, and then 24 urines and fecal specimens were analyzed [54]. The tests subjects diets were carefully controlled: "*The analysis shows that all four purines produced a marked rise in urinary uric acid and a small, yet noticeable increase in elimination of purine bases*" [54]. They summarize the six known human studies that all indicate that nucleoproteins appear to have the chief end product of uric acid in humans but not other mammals (they did not know about the Dalmatian breed). This same group would also later publish on observations of rats forming phosphatic stones in 1917 [55].

Conclusions

> "*But with regard to the material world, we can at least go so far as this-we can perceive that events are brought about not by insulated interpositions of Divine power, exerted in each particular case, but by the establishment of general laws.*"
>
> —William Whewell (1794–1866) [10]

We began the rise in science using Francis Bacon's notions of science and the interaction that science has with society. Francis Bacon (1561–1626) was a genius whose vision of science literally changed the world, and his legacy has gone through several revivals [56]: "*Now the true and lawful goal of the sciences is none other than this: that human life be endowed with new discoveries and powers*" (Aphorism 81) [7]. Bacon continued the theme further on using a powerful metaphor of insects, suggesting that "*Those who have handled sciences have been either men of experiment or men of dogmas. The men of experiment are like the ant; they only collect and use; the reasoners resemble spiders, who make cobwebs out of their own substance. But the bee takes a middle course; it gathers its materials from the flowers of the garden and of the field, but transforms and digests it by a power of its own*" (Aphorism 95) [7]. That he had faith in the boundless possibilities for the future is unquestioned. But he lived in the present, and the present medicine had little to offer stone sufferers: "*The truth, I believe, was that he had had a more serious illness than anybody supposed. In the beginning of March we learn from Chamberlain that he had a severe fit of the stone, 'which held him great pain two or three days.' But his illness appears to have lasted a good deal longer*" [2]. Bacon's legacy transcends his suffering from stones, however. We've spent much of this chapter discussing those who in the nineteenth century felt some admiration for his vision of science. Let's turn to Charles Darwin's autobiography, "*After I returned to England it appeared to me that …by collecting all facts which bore in any way on the variation of animals and plants under domestication and nature, some light might perhaps be thrown on the whole subject. My first notebook was opened in July 1837. I worked on in true Baconian principles, and without any theory collected facts on a wholesale scale*" [57].

Benjamin Winslow Dudley (1785–1870) is a typical early American medical saga but little heralded. He was born on April 12, 1785, in Virginia, but his Baptist minister father brought the family westward with his family to Lexington, Kentucky. In 1797 the 12-year-old Benjamin began his extended apprenticeship with the local physician, Frederick Ridgely. Following his mentor's advice, Dudley matriculated to the University of Pennsylvania where he graduated and received his M.D. degree in 1806. He noted the success of Philip Syng Physick who did perform some lithotomies and invented his own urinary catheter and surgical instruments (Physick was trained in London by John Hunter) [58]. He promptly returned to Lexington and practiced for about 4 years. He had more substantial plans including becoming a great surgeon and developing a medical school in Lexington. He showed his entrepreneurial spirit by investing in tons of flour and a flatboat to New Orleans and transported it to Lisbon where he made a substantial profit. He was able to finance an extended European extension of his education [59]. He studied and worked with Abernethy, Bayer, Cline, Sir Astley Cooper, Dupuytren, and Dominique Larrey. He certainly developed a profound interest in bladder stones and the lateral perineal lithotomy. He returned to Lexington to help reorganize the Transylvania Medical School that he had helped found. It had been recorded that he operated on 225 cases of bladder stone with only five deaths (better than Cheselden's outcomes). Dudley spent 33 years at Transylvania till he retired in 1850. He fought one duel with his colleague and subsequent lifelong friend, Dr. William Richardson, over another colleague, Dr. Daniel Drake [60]. James M. Bush who succeeded Dudley as professor of anatomy and surgery at the Transylvania Medical School published Dudley's outcomes in 1837 [61]. Two portraits, a bust of Dudley, and his surgical and lithotomy sets are all enshrined at the University of Kentucky's Transylvania's Special Collections section.

Reginald Harrison was one of those surgeons who listened to new surgical ideas and tried them. He was one of the first clinical practitioners in England to adopt the new ideas of Bigelow from Boston, litholapaxy. This was the second major surgical contribution from the United States back to England, the first being laparotomy for benign cystic ovarian disease that was pioneered by another frontier surgeon Ephraim McDowell in 1809. McDowell also had learned lithotomy, probably not the lateral approach from John Bell during the 2 years McDowell spent in Edinburgh (1972–1974). Two years following his first ovariotomy on Jane Todd Crawford (related to Mary Todd Lincoln), McDowell performed a successful perineal lithotomy on a 17-year-old youth named James Knox Polk [62]. The surgery was a success but Polk developed infertility following the surgical procedure, and he and his wife Sarah were never able to have children [63]. But back to Reginald Harrison, he wrote an influential treatise on the use of litholapaxy and evacuators in 1883 championing the American method in England [64]. Harrison takes great efforts to not to minimize the contributions of others, but rightly points out the clearance of the bladder of all fragments following a lithotrity and the advantages of inhalational anesthesia. He discusses all the modifications that are being discussed about evacuators, and he presented his results in 28 litholapaxies. The stones ranged in weight from 100 to 1,200 grains and in these cases he had two deaths. He spends a good deal of time discussing the high-risk patients, including older males with large prostates, and those with severe cystitis [64]. He actually presents data on what was called "urethral fever" which resulted in the death of patients from even simple manipulations [65]. This is of course following the rise of bacteriology championed by Louis Pasteur, antiseptic surgery by Joseph Lister, and the monumental accomplishments of Robert Koch (Nobel Prize in 1905).

Benjamin Disraeli was a writer and civil servant similar in some aspects to Francis Bacon, but he oversaw the latter's vision of the future of science into a reality. Railroads crisscrossed England and the United States, electricity had been harnessed, electric illumination had been introduced, and photography was widely being utilized to document individuals and events, such as the American Civil War as well as Sir John Herschel's beloved nebulae. They both became cabinet members and went on to become Prime Minister. After a short year's tenure in 1868, he became close to Queen Victoria, especially following the death of Prince Albert in 1861. He returned to the Prime Ministry again in 1874 and remained in power till 1880. The illness of Disraeli is not altogether clear. He suffered from gout, bronchitis, asthma, and he had kidney problems (considered Bright's disease) [66]. He was attended by a number of physicians including Sir Richard Quain (1816–1898). Joseph Kidd (1824–1918) was Disraeli's long-standing physician. Disraeli also asked to see Sir William Jenner, who came to see him at the Queen's request. Finally a young Scottish physician, Dr. John Mitchell Bruce (1846–1929), was finally called. He was in near constant attendance to Disraeli during his last 10 days of life [67]. Benjamin Disraeli died before the science of medicine could help the clinical practice of medicine.

Sir James Paget (1814–1899) was both a surgeon and a pathologist. He is most well known for his 1851 *Lectures on Tumors* and his 1853 *Lectures on Surgical Pathology*. James also became the curator for the Royal College of Surgeons of London in 1836 and a fellow of the Royal Society in 1851. He noted, "*Let me tell you of a symptom which must make you especially cautious if you have to catheterize elderly or old men. If they are passing large quantities of pale urine of very low specific gravity, whether containing a trace of albumin or not, they will be in danger from even the most gentle catheterization*" [68]. His brother Sir George Paget was also a well-known physician and became the Regius Professor of Medicine (Physic) at Cambridge University in 1872. He was called to treat one of the towering scientists of the nineteenth century, James Clerk Maxwell. Maxwell who also graduated from Trinity College in 1854 developed the mathematical system to explain much of Michael Faraday's electromagnetic work. He epitomized the notion of the nineteenth-century scientist, those who inherited the tradition of Bacon envisioned by Whewell. Albert Einstein utilized Maxwell's dynamical electromagnetic field theory as the foundation of his 1905 special theory of relativity [69]. Maxwell also invented and took the first color photograph. Maxwell's death was completely unexpected. He wrote to Stokes in August of 1879 that he had sudden abdominal pain with nausea, but he apparently regained his strength. But by October, it was apparent that he had a much more serious illness. The Regius Professor Sir George Paget was called, and he was informed that he had only a few weeks to live because of an abdominal malignancy. Paget put this diagnosis on his death certificate [70].

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22 Fictitious Stones and Sir William Osler

Introduction

> "*I observe the Physician, with the same diligence, as he the disease; I see he feares, and I feare with him: I overtake him, I overrun him in his feare, and I go the faster, because he makes his pace slow; I feare more, because he disguises his feare, and I see it with the more sharpnesse, because hee would not have me see it. He knows that his feare shall not disorder the practise, and exercise of his Art, but he knows that my feare may disorder the effect and working of his practise. As the ill affections of the spleene, complicate, and mingle themselves with every infirmitie of the body, so doth feare insinuat itself in every action, or passion of the mind; and as wind in the body will conterfet any disease,* ***and seem the Stone****, and seem the Gout, so feare will conterfet any disease of the Mind*." [1]
>
> —John Donne, 1624

Kidney stones are obviously associated with much pain and suffering and have engendered this particular disease condition with the stigmata regarding pain medications. Both the presentation and treatment of this rather painful affliction is associated with the potential for abuse. This of course renders care for all such individuals suspect to those routinely dealing with stone patients. The history of narcotics is another fascinating saga that directly relates to stone disease. The name "narcotic" was derived from the Greek word for stupor. Indeed euphoric bliss is typically used as the archetype of what many a chemical utopia might be like. One example was "*Soma*" in Aldous Huxley's *Brave New World* which was depicted as a cross between a nonaddictive opioid and a hangover-less tranquillizer [2]. Huxley's Utopians enjoyed the empty, imbecilic happiness of their drug when not working for the state. Also noted at the beginning of Philip P. Dick's novel *Do Androids Dream of Electric Sheep?* is the hero Rick Deckard sleeping next to his significant other who is addicted to direct electrical cortical stimulation and famously portrayed by Harrison Ford in Ridley Scott's on-screen adaptation called *Blade Runner* [3, 4]. Addiction and the use of narcotics are mainstream occurrences that no longer are revolting or intolerable to our society, though still looked down upon.

"*Presently she cast a drug into the wine of which they drank to lull all pain and anger and bring forgetfulness of every sorrow*" stated Homer in the Odyssey when discussing Telemachus from the ninth century before the current era [5]. The Sumerians certainly cultivated poppies and probably isolated opium from the seed pod, calling it the word for joy, "*gil*" [6]. The Greek physician Hippocrates (c460–c377 BC) discounted the belief in the literal magical attributes of opium, an indication perhaps of the high reputation of the opium poppy, *Papaver somniferum* in classical antiquity. Hippocrates acknowledged the benefits of opium poppy juice (Greek *opos*, means juice) as a narcotic and styptic in treating internal diseases, diseases of women, and epidemics. Hippocrates also noted the excellent nutritive properties of the poppy seed. Galen of Pergamum wrote about the juice of the poppy "*which physicians are in the habit of calling opium.*" He recommended its use as a

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cure for headaches, deafness, epilepsy, asthma, coughs, **colic**, fevers, women's problems, and melancholy. The *spongia somnifera* was an opium soaked sponge that was used to relieve the pain of lithotomy and other ancient surgeries [6]. By the eighth century the poppy was being cultivated in India and the Far East, and opium addiction was rapidly introduced back into Asia Minor and Europe. The early Renaissance iatrochemist and physician, Paracelsus, claimed "…*I possess a secret remedy which I call laudanum and which is superior to all other heroic remedies*" [7]. Thomas Sydenham was happy to pay tribute to Providence praising the narcotic "*Among the remedies which it has pleased Almighty God to give to man to relieve his sufferings, none is so universal and so efficacious as opium*" [6].

Friedrich Sertürner was born near Paderborn in the Westphalia region of Germany on June 19, 1783. He apprenticed at the age of 16 as a pharmacist to Cramer. He was allowed to set up his own chemistry laboratory in the basement of the pharmacy. He worked in the shop during the days and in his laboratory in the evenings. After 4 years in training, Sertürner isolated an active ingredient from the poppy plant, source of opium which he called morphine [8]. He originally began to soak the opium in various alkaline solutions. In the ammonia solutions he was able to isolate a precipitate that he could purify and crystallize. He injected both the solution and the precipitate to dogs showing that the solution had no effect, but that the precipitate caused both drowsiness and pain relief. He published his findings in 1806 and moved his laboratory to Einbeck. In 1817, Sertürner changed the name of his compound to morphine, after the Greek god of dreams, Morpheus. In that same year, Joseph Gay-Lussac reported upon Sertürner's discovery, and the Institute de France awarded him a two-thousand-franc prize. He was also given an honorary Ph.D. by the University of Jena. Sertürner died on February 20, 1841, probably of a myocardial infarction [6]. Not only did the discovery of morphine change our management of pain, but it was also the first alkaloid to be successfully isolated, though ironically a pharmacist, Derosne, also did isolate the morphine-like substance 14 years prior to Sertürner but he failed to purify it, thus failing to gain the prize [6].

Codeine was the next isolated alkaloid a few years after morphine [6]. The rise of physiologists, such as Claude Bernard, resulted in the investigation of opioids for sedating animals, which spread quickly to human use during surgery [9]. The hollow-bore needle allowed for intravenous instillation and more rapid onset of analgesia, but more intense euphoria as well was developed in the 1850 s. Heroin, the hydrochloride of diacetylmorphine, was discovered by acetylation of morphine. Heroin, in pharmacological studies, proved to be more effective than morphine or codeine. The Bayer Company started the production of heroin in 1898 on a commercial scale [6]. In the early 1910s morphine addicts "discovered" the euphoric properties of heroin, and this effect was enhanced by intravenous administration. Heroin became a narcotic drug and its abuse began to spread quickly. Restrictions on its production, use, and distribution were regulated by international treaties. The total ban on heroin production was also proposed. As a result of the strict regulations, the production and consumption of heroin showed a significant decrease after 1931. Meperidine became the first structurally different opioid to be developed in 1939 followed by methadone in 1946 [6]. In 1942 the first opioid antagonist was synthesized by Weijlard and Erikson called nalorphine (N-allylnormorphine) [10].

Sir William Osler

Sir William Osler's influence on medical practice continues to be felt throughout modern medicine, even including surgical specialties such as urology. His textbook of medicine, *The Principles and Practice of Medicine,* was the cornerstone of medical education at the turn of the twentieth century [11]. The writing and organization of his textbook was unique in that era, and his emphasis upon the science behind the practice of medicine was foremost. Dr. Osler was also known as the physician's physician because of his mastery of medical knowledge, his interpersonal skills, and not the least for his unbridled sense of humor. Many pranks perpetrated by Osler on his colleagues, students, and friends have been widely quoted in the burgeoning literature of Oslerania [12].

William Osler suffered from recurrent bouts of urolithiasis and this is not widely known [13]. The purpose of this investigation is to provide details regarding Dr. Osler's stone episodes and put into perspective his own experiences with the writings from his *magnum opus*, his textbook. Since Osler formed stones after the first edition, his understanding of the suffering of patients with this disease evolved during the seven editions that he personally wrote. One can readily appreciate the incredible insight this distinguished father of modern medicine was capable of evoking.

Dr. Osler's first edition of *Principles and Practice of Medicine* was scrutinized for specific details on urolithiasis. His concepts and writings were cross-referenced for a thorough review of all his extensive publications. In addition, Dr. Osler's collected works such as public addresses and speeches were also evaluated [14]. Finally, data was obtained from the modern biography of Osler by Michael Bliss and Harvey Cushing's two-volume Pulitzer Prize-winning manuscript [15, 16]. All documents concerning his episodes of colic were cross-referenced to any writing Dr. Osler presented in his subsequent revised editions of his textbook.

Osler's Fictitious and Real Encounter

Professor Osler was the first chief of medicine at the Johns Hopkins University. He published the first edition of his *Principles and Practice of Medicine* in 1892. This textbook sold remarkably well and went through many reprintings due to its unprecedented popularity [15]. Osler's section on urolithiasis reflects the style of the textbook throughout. He is succinct, very well organized, and tries to maximize the science behind the clinical recommendations. He defines urolithiasis as "*the formation in the kidney or its pelvis of concretions, by disposition of certain of the solid constituents of the urine*" [11]. Modern stone formation theories are hardly more succinct or different from this claim. Under the section on the etiology and pathology of stone formation, Osler states that there are three types: (a) small gritty particles, (b) larger concretions, and (c) dendritic forms. He further categorizes stones by chemical composition as follows: uric acid—"*by far the most important, oxalate of lime- forms in mulberry-shaped, studded with points and spines, phosphatic calculi- composed of ammonio-magnesium phosphate with carbonate of lime, and rare forms- including cystine, xanthine, carbonate of lime, indigo, and urostealith*" [11].

Osler's first kidney stone episode has received the most attention, for one of his former residents, Thomas B. Futcher, had the dubious honor of becoming the "Professor's" physician [17]. On the evening prior and morning of December 31, 1904, Osler experienced repeated episodes of progressively severe left flank pain. He correctly diagnosed his own condition and apparently passed the stone on that morning. In a prank on Futcher, or perhaps to impress his junior colleague on the size of stone that the "old man" might pass, he provided evening and morning voided urines for urinalysis with a few hefty stone specimens picked up from his own walk way on his way to the hospital (1 West Franklin Street). Dr. Futcher correctly identifies the fictitious stone as quartzite and eventually published, perhaps the first case report of a patient presenting with a fictitious calculus in the Archives of Medicine in 1949 [18]. In the write up, Futcher describes the Professors microscopic urinalysis as follows: "*No casts; an occasional red blood cell seen; numerous oxalates; no uric acid crystals. No true renal calculi found in either specimen. One bottle contained 3 and the other 2 quartz stones gathered from the gravel walk*" [17]. Johns Hopkins University has not kept the nefarious stone in its archives or museum, and the walkway no longer exists [18].

Osler himself speculates that the stone was uric acid but there is no evidence that a full chemical analysis was performed [19]. His textbook is very accurate on the clinical manifestations of renal colic. He iterates four primary symptoms as follows: (1) "*pain- usually in the back, dull to severe, may come in paroxysms*," (2) hematuria, "*seldom profuse, as in cancer. Aggravated by exertion and lessened by rest*," (3) "*pyelitis- (a) pain initiated by a heavy chill followed by fever (104 to 105°), followed by profuse sweating. (b) purulent pyelitis has pus in the urine*," and (4) pyuria, "*some instances where pus appears in the urine continuously*" [11]. Osler proceeds with a differential diagnosis and features of renal colic that aid in making the correct diagnosis. This includes referred pain to the testicle, retraction of the ipsilateral testicle, and the association with hematuria [11].

Osler was considered by his peers as a therapeutic nihilist. In fact, he believed in therapies that could have documented beneficial outcomes that could be measured. He expostulated nine therapeutic measures for treating patients with renal stone disease [11]. Pain relief can be experienced by a hot bath. Next, morphia should be given hypodermically for very intense pain. Inhalation of chloroform may be necessary in severe cases. Local applications are "*sometimes grateful*" such as poultices or hot clothing. The patient may freely drink hot lemonade, soda water, or barley water: "*The patients should live a quiet life*." The patient should remain hydrated, "*keep the urine abundant and alkaline*." "*Diet should be carefully regulated*" [11]. Dr. Osler does not provide the details of the referred dietary regimen, but this is something of a scientific abyss currently. He does conclude by citing that "*surgical treatment has advanced rapidly and resorted to only when the attacks of pain interfere with the occupation of the patient, or when pyelitis or pyelonephritis has been exited*" [11].

Sir William Osler's subsequent bouts with stone disease occur during his tenure as the Regius Professor of Medicine at Oxford. Again, the colic attacks began in the winter of 1910, but there are no practical jokes with these episodes. In his own words, he notes periods of complete freedom from pain of 2–3 h to as many as 8–10 h apart. He carefully notes three types of disturbing sensations during these episodes of colic. First, a dull, steady localized pain "*the situation of which could be covered by a penny*." Next, "*while free of pain there were remarkable flashes, an explosive sort of sensation, not actually unpleasant*." Finally, "*out of the steady pain came the paroxysm, like twisting, tearing hurricane*" [20]. This second episode is detailed by Bliss as a "*rocky experience*" that took a week of squirming before it subsided [15]. Dr. Osler considered surgical intervention and consulted with a surgeon. X-rays were taken but no records of these remain, but they would have shown no stone if indeed they were uric acid as these are radiolucent. He theorized that the gout was at the bottom of his troubles and that he would have to live off "*distilled water and grits*" [19]. Throughout the entire year of 1910, Osler would comment to his friends and acquaintances that he continued to feel "*loose rocks rattling*" at the end of busy days [15]. He carefully documented the use of morphine for his bouts of colic—"*God's own medicine*" [19].

An autopsy was performed at Osler's own request after his death on December 29, 1919. He had written previously that he wished that he could be in attendance at his own autopsy. A. G. Gibson and an assistant performed the examination as was custom of the time in the Osler home at #7 Norham Gardens in Oxford. The kidneys were described as being in good condition. Pinpoints of urates were noted to be studding the calyces [21]. Throughout the seven personalized-revised editions of the "*Principles and Practice of Medicine,*" Dr. Osler continued to maintain his unadorned methods of expressing the fundamentals of disease [22].

Hypochondria

> "*Sharp belchings, fulsome crudities, heat in the bowels, wind and rumbling in the guts, vehement gripings, pain in the belly and stomach sometimes after meat that is hard of concoction, much watering of the stomach, and moist spittle, cold sweat…cold joints…midriff and bowels are pulled up, the veins about their eyes look red, and swell from vapous and wind…their ears sing now and then, vertigo and giddiness come by fits, turbulent dreams, dryness, leanness…grief in the mouth of the stomach, which maketh the patient think his heart itself acheth*." [23]
>
> —Robert Burton, 1621

"*Melancholy may be defined as a state of mind in which man is so out of touch with his environment that life has lost its sweetness*"—thus begins Osler in his review of Burton and his works [24]. Osler considered Robert Burton's work as the "*greatest book of psychiatry that had ever been written by a layman*." It was noted by Bergen Evans and George Mohr that it took over 300 years for Robert Burton's Anatomy of Melancholy to gain the notice of psychiatrists [25]. Osler also noted that "*No book of any language presents such a stage of moving pictures*" [24]. Burton was a contemporary of both Sydenham and Harvey, bridging the world from Renaissance to Enlightenment. Burton most likely suffered from melancholy himself, hating his early life in academia at Oxford. Burton interestingly never defined melancholia but used quips of others: "*It is symbolizing disease, expressing itself according to the personality and environment of the patient in diverse symptoms, of which fear and sorrow 'out of proportion with known causes' are the chief. Those afflicted are restless, emotionally unstable, inclined to be greedy and covetous, ill-tempered and aggressive. They are particularly disturbed in their sexual relations, using the term in its widest possible sense*" [23]. This is of course hugely in advance of Sigmund Freud and psychoanalysis and almost 300 years before he published on Narcissism in 1914 [26]. Evans and Mohr noted that Burton distills four causes for the pathology of melancholy. First is heredity, it can be inherited or runs in families. Second is a lack of affection in childhood which he reports is closely associated with sexual frustration (very Freudian again) [25]. Third is best described in Burton's own words, "*self love might be regarded as the fountainhead of all melancholy. For love of self prevents love of others. Unloving, the man feels unloved; and unloved, insecure. Insecurity breeds fear, and fear, preying upon the mind, distorts the imagination 'which, misinforming the heart, causeth all these distempters*'" [23]. The final cause of melancholy is the maladjustment of the individual to society; they do not respond appropriately [25]. Burton even guides the modern physician into the realm of treating this malady: "*The physician who desires to help them must first rectify the passions and perturbations of his own mind, so that he may not mislead them and so that he may endure with patience and equanimity their emotional vagaries*" [23]. This is so close to Osler's own philosophy of medicine that he decanted for graduates of the University of Pennsylvania in 1889 forming almost his motto, Aequanimitas [27]. Burton's final admonition for therapy also requires mentioning, "*The personal influence over the patient, is the 'notable secret' of the success that have been achieved in the care of sickness*" [23].

We have seen that certain types of stone-forming patients obviously suffer from melancholy and hypochondria. These associations are most prevalent in the fictitious group that Osler himself jokingly participated by placing his pebbles in for Futcher's benefit. Osler's omnivorous historical and bibliographic interests brought him to Richard Burton's Anatomy of Melancholy.

Perhaps it would be appropriate here to digress a bit into two rather famous historical characters that both fascinated Sir William Osler, but of who's suffering and undeniable relationship to Burton's Melancholy he ignores. They have little relationship to urolithiasis, sadly, but touch on the problems mentioned by Burton and lead us to the psychological problems that do touch upon the chronic nature of some stone sufferers. Charles Darwin was a scientist whose legacy touches virtually every aspect of modern biology and whose life was every day touched by his nearly incapacitating illness. Darwin was himself substantially aware of his ill health, and he kept a Diary of Health from July 1, 1849, till January 16, 1855 [28]. His obituary in 1882 British Medical Journal stated he had suffered all of his life from "a *condition of the nervous system reacting upon the digestive organs which necessitated great care*" [29]. His friend Thomas Huxley (also a hypochondriac) noted that his fried *suffered* from Chilean fever and forever left its mark. Dr. William W. Johnston wrote an early article entitled *The Ill Health of Charles Darwin: Its Nature and Its Relation to His Work* in 1901 [30]. Dr. George M. Gould followed with his book *Biographic Clinics: The Origin of Ill-health of De Quincey, Carlyle, Darwin, Huxley, and*

Browning in 1903 [31]. Saul Adler recalls the account from Darwin's Journal of Researches when he was bitten by "the great black bug of the Pampas" and hypothesizes him contracting Chagas' disease [32]. John H. Winslow wrote an article called *Darwin's Victorian malady: evidence for its medically induced origin* in 1971 [33]. We do know that Charles Darwin was at first a huge fan of Dr. James Manby Gully's *The Water-Cure in Chronic Disease* though he came to doubt much of the science in this method. He commented "*I cannot but think in my beloved Dr. Gully that he believes in everything*" [34]. Darwin the quintessential skeptic could not long accept that which he could not test. As Brian Dillon noted, "*Darwin's self-identification as a dyspeptic was thus utterly conventional one for the time: the illness is as thoroughly cultural as the related afflictions of melancholia, hysteria, nervousness and hypochondriasis itself*" [34].

Florence Nightingale is the second intriguing Victorian that interested Osler, but of whose illness and its profound effect upon her life is virtually ignored [35]. She had returned from her widely heralded exploits in the Crimean War a national hero in 1856. She was immortalized in The Lady and the Lam: "*She is a 'ministering angel' without any exaggeration in these hospitals, and as her slender form glides quietly along each corridor, every poor fellow's face softens with gratitude at the sight of her. When all the medical officers have retired for the night and silence and darkness have settled down upon those miles of prostrate sick, she may be observed alone, with a little lamp in her hand, making her solitary rounds*" [36]. Also Longfellow followed suit:

> *Lo! in that house of misery*
> *A lady with a lamp I see*
> *Pass through the glimmering gloom,*
> *And flit from room to room.* [37]
>
> —Henry Wadsworth Longfellow
> (1857 *Santa Filomena*)

Yet Florence became a virtual recluse, doing her work and sending her minions out to carry out the work of reform that so enveloped her second career. She also sought the water cure and followed Darwin to the spas. Sir Edward Cooke in 1861 described her as a "hopeless and incurably invalid" though he remained amazed at her energy and accomplishments [38]. Nightingale's worst times were following 1861 when she became completely bedridden until about 1870. Physicians speculate that she might have contracted brucellosis, but her hypochondriacal overtones are unmistakable. Dillon also notes poignantly "*She was in many ways the saint that Victorian sentiment wanted her to be, and other respects a monster of self-belief, self-delusion and expertly deployed enfeeblement*" [34]. As she improved late in life, she actually became obese and an amiable as she progressed to senility, but Thomas Edison recorded her voice before she died, leaving us a lasting, haunting impression of the Lady with a Lamp [39].

John Griffith Chaney was born on January 12, 1876, in San Francisco but changed his name to Jack London and became a social activist, journalist, and great American writer. He was a hugely successful author of *The Call of the Wild, White Fang,* and the *Sea Wolf*. He began as a serious student at Berkeley but dropped out for a life of adventure [40]. He traveled to the Klondike, became a cannery worker, and bought a boat to become an oyster pirate. He was stricken with stone disease and suffered from recurrent attacks of colic which undoubtedly made him use doses of morphine regularly. He probably became addicted to morphine in the last 3 years of his life. The official biography of London at the Huntington Library concludes that "*his death has still not been satisfactorily explained*" [41]. His death certificate gives the cause of his death as uremia, following acute renal colic, a type of pain often described as the "*the worst pain ever experienced*" [41]. The cause of his interstitial nephritis might well have been caused by his chronic use of self-administered "corrosive substance" mercuric oxide that he used to treat yaws and possibly gonorrhea [42].

Drugs and Doctors

Opioids, particularly mu-receptor agonists, produce the psychological effects that are associated with addiction. There are more mu-receptors in the brain than in the spinal cord, consistent with the current knowledge of the pathophysiology of the addiction process. Euphoria and reward produced by the mu-agonists are currently thought to stimulate the dopaminergic neurons in the ventral tegmental area of the midbrain. Prescription opioids are highly sought after by addicts. It is currently estimated that the street value of prescription narcotics is greater than marijuana and heroin but remains second to cocaine [43]. The Drug Enforcement Agency has estimated that about 1/3 of illegal drug traffic comes from prescription narcotics [44].

It appears in the early annals of the twentieth century physicians had rather a complacent attitude towards narcotics. In the 1840 s the average consumption of opium in the USA was 12 grains and increased to 52 grains by the turn of the century (400 % increase) [45]. Dr. Alexander Lambert the president of the American Medical Association in 1920 urged physicians to stop "*a few renegade and depraved members of the profession who, joining with the criminal class, make it possible to continue the evil and illicit drug trade*" [46]. Sir William Osler wrote up an interesting case of a 40-year-old man who died of an opioid overdose in 1880. He noted that the "bronchi contain frothy serum" and might be the first description of this effect by drugs [47]. Osler would go on to discuss addiction to narcotics in his *Principles and Practices of Medicine*. He put "morphinism" immediately following alcoholism in his textbook and singled out women and physicians as the two most frequently effected groups [11]. Osler was actively involved in the treatment and follow-up of his colleague and chief of surgery at Johns Hopkins, William Stewart Halsted [48]. Halsted like Sigmund Freud was experimenting with cocaine and became addicted to narcotics. He underwent a profound personality change, and his life and career also suffered tragically [49]. Osler faced the treatment of addiction in his textbook offering no hopeful prognosis and recommended only isolation, systematic feedback, and gradual drug withdrawal. He warns that "*Even under the favorable circumstance of seclusion in an institution and constant watching by a night and day nurse, I have known a patient to practice deception for a period of three months*" [11]. One wonders if he was discussing Halsted again.

We've discussed briefly Osler's bouts with urolithiasis, but now let's turn to his suffering in the winter of 1910 when he was Regius Professor at Oxford to sample his opinion on the use of narcotics. He sent a postcard to his friend and colleague from Hopkins, Henry M. Thomas: "*I am in bed with another attack of renal calculus- rt. side. You remember the one 8 years ago in which I passed the unique quartz stone. This has lasted longer and I have enjoyed the luxury of two hypodermics. I am writing flat on my back which improves my handwriting*!" [19] This is the typical jocularity one finds in Osler's letters. He wrote to Marjorie Futcher and he also wisecracks about his suffering as follows: "*Tell T.B. [Thomas B. Futcher] that the enemy left me yesterday morning (composition* $C_2H_{10} + N_{20}S_2$*). I had a miserable week but managed to get thro. in fairly good spirits and am thankful that it is over. I had an X-ray taken to see if this is a quarry or only diamonds*" [19]. But Osler was serious enough during this attack of colic to carefully record his suffering in his daybook:

> Monday 17th. 5 [29] in eve. a twinge of pain in right side, thot. it was in bowels.
> Tuesday 18th. 8 AM. very severe attack, pain in right side, nausea, vom, sweats, ¼ [gr] morphia gave relief.
> Wednesday 19th. Return slight. in eve.
> Thursday 20th. Bad attack middle day. Morphia again. Good night.
> Friday 21st. Slight attack this day.
> Saturday 22nd. Slight attack this day.
> Sunday 23rd. 1 [29]-5 [29] steady pain and down groin- comfortable all night.
> Monday 24th. 8 [29] passed a uric acid calculus- and very well tho shaken & used up [19].

Osler discussed his colicky episodes in two treatises and talks that followed. The first was in March of 1910 when he gave the Lectures at the Royal College of Physicians in London. Here he mentioned his use of "*God's own medicine- morphia*" [19]. The second paper he never completed or published. It was called "*An auto-clinique*" and begins with "*Plato's remark that no physician is fit to treat a disease that he has not had.*"

He moves on to state that "*there is more than a grain of truth in the statement and we look with very different feelings upon a disease to which our own machinery is liable*" [19]. Yet by all accounts Osler was sparingly applying G.O.M. to his own suffering quite possibly aware of the addictive potential from his earlier encounters with Halsted. In addition, he may well have recalled an early encounter with a narcotics overdose resulting in suicide.

The Harrison Narcotic Act of 1914 was introduced by Representative Francis Burton Harrison of New York when American addiction reached an all time high of 1/400. The law was tightened in 1918 and addiction rates fell, as several physicians were arrested and tried for treating addicts. Heroin was outlawed in the USA in 1924 and the Uniform State Narcotic Act in 1832 further contrived tight federal control of narcotics. The Controlled Substances Act of 1970 mandated adding warning labels to potentially addicting products [50]. It is interesting that Coca-Cola® had cocaine in small quantities when originally invented by John Pemberton at the Eagle Drug and Chemical Co. in Columbus Georgia. It was derived as a prohibition era variant of coca wine which Pemberton claimed cured many diseases. His first add appeared on May 29, 1886, in the Atlanta Journal [51]. Law enforcement and treatment policies of the Nixon administration are often credited with ending the epidemic of heroin addiction that rose in America's cities in the 1960s. In this article it is argued that although the interventions did in fact cause a major change in heroin distribution and use, the epidemic did not end in any simple way. The decline in heroin and increase in methadone that resulted from the Nixon policies lead to a shift for many addicts in both clinical and street settings from one narcotic to another. There was a two-day symposium in 2002 with the intriguing theme "*Opioids, the Janus Drugs, and the Relief of Pain.*" Janus, the dual-faced Roman god, was chosen to symbolize the promise and problem that opioids represent for both users and practitioners [52].

Munchausen's Syndrome

One of the first reports on patients with factitious diseases not surprisingly arises out of the history of medicine and war. In 1843 Hector Gavin wrote a book entitled *On Feigned and Factitious Diseases* that truly summarized a problem that causes such controversy today [53]. As war increased the social ramifications of the injured soldier, so too did the risk of soldiers who were manifestly faking an illness: "*Disease has been simulated in every age, and by all classes of society. The monarch, the mendicant, the unhappy slave, the proud warrior, the lofty statesman, even the minister of religion, as well as the condemned malefactor, and boy "creeping like a snail unwillingly to school" have sought to disguise their purposes, or to obtain their desires, by feigning mental or bodily infirmities*" [53]. The French Ordinance of 1831 was the first attempt to classify infirmities of the injured soldier. Hector comes up with four categories as follows:

1. Feigned or purely fictitious diseases
   (a) Pretended
   (b) Simulated
2. Exaggerated diseases
3. Factitious diseases
4. Aggravated diseases [53]

The kidney stone patient can be present in any of these categories. He noted that 22 out 5,743 admissions had feigned stone disease or gravel: "*One may feign the symptoms of a disease, without any disease existing- or else may excite a state of real but temporary disease, in order to have it taken for a more chronic or permanent disease*" [53]. Though he notes that pain is one of the easiest of symptoms to present with, he documents the necessity of suspicion: "*In affections of the kidneys and bladder, besides other symptoms, such as nausea and vomiting, there is ardor urinae- high-coloured urine, depositing a sediment, and sometimes mixed with blood; sometimes there is suppression- sometimes dribbling with dysuria*" [53].

In 1951 Richard Asher described a syndrome of factitious disorders that he proposed "*the symptom* *be respectfully dedicated to the baron* [Karl Friedrich von Munchausen]" [54]. Munchausen (1720–1787) was a German aristocrat who fought with the Russians and spent his life telling self-aggrandized stories leading to a book by Rudolf Erich Raspe called *Baron von Munchausen's Narrative of his Marvellous Travels and Campaigns in Russia* [55]. Asher described these patients as being medically difficult, because they are more devious than the doctor and often refuse therapies "against medical advice." He described three varieties of Munchausen's syndrome: acute abdominal type, the hemorrhagic type, and the neurologic type. It is the first that is of interest to our discussion of urolithiasis. It is important that clinician recognize that patients with this syndrome often have true physical illnesses that need appropriate treatment as well [56].

Hyler and Sussman reviewed this condition and identified six features that are commonly associated with Munchausen's syndrome. First pseudologia fantastica refers to their pathological lying. They will often report multiple hospitalizations or surgeries that are fictitious. These patients are typically sophisticated; they can give "*textbook histories*." They are disruptive; they make excessive demands, can be unruly making a scene for any pretense, and often make complaints. These patients have a tendency to sign out the hospital "*against medical advice*," AMA. They demand for a certain type of medication, particularly a specific narcotic serves as a red flag suggesting the patient might be prone to addiction. These investigators noted that these patients typically do not have visitors; they are loners and will not allow others to participate in the sickness [57]. Supposedly the incidence of Munchausen syndrome peaks in young-to-middle-aged adults, most typically between 30 and 40 years of age. Caucasians predominate in ethnicity, and most are loners, having failed at marriage and inability to hold a job [57].

Patients with Munchausen's syndrome are thus stereotypically quite easy to spot; however, busy emergency rooms often send them to urologists for further evaluation and will often send them off with just a few narcotic doses to allow them to get in to see the specialist. A young female with bilateral fictitious stones presented a quandary to a European urology department. She actually got admitted and further evaluation disclosed the addiction disorder and prompted the psychiatric evaluation [58]. The abdominal type often fakes stone disease symptoms using the excuse that their stones are radiolucent. Prior to the era of non-contrast CT scans, these patient's would use the excuse of being intravenous contrast allergic, thus avoiding the intravenous pyelogram [59]. Stone disease represents a real dilemma in managing these patients, because they are so often successful in manipulating the medical system [60]. It has been reported that these patients demonstrate tremendous willingness to undergo procedures which can cause complications, such as scarring of the ureter and hydronephrosis. These patients are masters of manipulating these untoward complications back to even more visits and narcotic consumption. Gluckman and Stoller also reported on some of the urologic aspects of patients presenting in the modern era. They are typically quite versed with medical terms, and they will often now complain of high fevers at home to increase the criticality of their situation. This makes the emergency management take a more serious consideration of these patients [61]. No society is apparently free of this masquerade of fictitious stone disease with several cases being reported in India [62].

Drugs and Stone Disease

> "*If we could sniff or swallow something that would, for five or six hours each day, abolish our solitude as individuals, atone us with our fellows in a glowing exaltation of affection and make life in all its aspects seem not only worth living, but divinely beautiful and significant, and if this heavenly, world-transfiguring drug were of such a kind that we could wake up next morning with a clear head and an undamaged constitution - then, it seems to me, all our problems (and not merely the one small problem of discovering a novel pleasure) would be wholly solved and earth would become paradise*." [2]
>
> —Aldous Huxley

Though opium has long been used and abused, very little information was available about this ancient narcotic and its relationship to stone formers until very recently [63]. This study was performed in Kerman city with a population of 700,000 inhabitants in south-east Iran. Opium use and addiction here is quite popular. The study involved comparing a group of stone-forming patients with a group of non-stone-forming controls. 450 urolithiasis patients with at least two episodes of colic were evaluated and 157 (34.88 %) were opium addicts. In the 340 non-stone formers, only 16 (4.70 %) were addicts. The investigators followed up on the stone-forming opium addicts. In those with addiction less than 5 years only 15 (9.55 %) were stone formers compared to 53 (33.75 %) with addiction >5–10 years and 89 (56.68 %) addicted greater than 10 years. There was a statistically significant correlation between the duration of addiction and the renal colic rates. The anatomical distribution of stones was identical in the addict group versus controls but also noted was that the upper tract rate of damage was higher in the addict group perhaps indicating more interventions or association with infection. There was no significant gender association in this study, though men formed stones almost 3:1 versus the females, typical for less industrialized nations [63]. It appears that painful stone episodes are clearly associated with addiction in the Iranian study, which was also suggested in earlier studies in England [64]. Unanswered however is which problems increase the risk of the other; does pain medication increase the risk of presenting for more pain medication? They conclude with a caution about addicts presenting to hospitals seeking more narcotics but fall back on the mandate of the physician to alleviate suffering.

The Opium Smoker

I am engulfed, and drown deliciously
Soft music like a perfume, and sweet light
Golden with audible odours exquisite
Swathe me with cerements for eternity
Time is no more, I pause and yet I flee
A million ages wrap me round with night.
I drain a million ages of delight
I hold the future in my memory [65].

—Arthur Symons

The prevalence of substance abuse in the USA is about 6.1 %, and this is an increased to 9.3 million Americans in 1999. One common recommendation from the emergency literature is to profile patients presenting with acute pain, like stone formers [66]. Drug addicts tend to insist on specific medications or are allergic to everything but their "choice" of narcotic. These fictitious patients tend to be younger and the mean age is 34.3 years. These patients are resource intensive; they visit an average of 12.6 emergency rooms annually. They will go to an average of 4.1 different institutions to support their habit. They use on average 2.2 different aliases. In some instances these patients can take up to 20 % of all emergency room time, limiting the availability of valuable resources to other truly sick patients [66]. There is also a compelling medical reason for identifying this drug-seeking behavior, because more than 50 % of patient who sought treatment for or died of drug-related problems in 1989 were abusing prescription drugs. The cost of this drug problem in America has been estimated to be $100 billion in 1992 [66].

Evaluation of a patient suspected of fictitious presentation involves recognition of the possibility of addiction, looking for the telltale signs, and evaluating carefully with the correct radiologic verification. These patients tend to be increasingly difficult to identify from real stone patients as they too are aware of the emergency providers profiling, but several clues predispose to making an accurate diagnosis prior to the patient depleting the emergency department of narcotics. Often the patient will state they form "uric acid" stones knowing that these are radiolucent and will not show up on screening K.U.B.s [67]. The patient is usually "allergic" to intravenous contrast agents of all types. The severity of the patient's pain is out of proportion or overdramatized by them while lacking the visceral signs associated with severe ureteral colic, i.e., diaphoresis, nausea, and vomiting [68]. The patients usually can manipulate his/her urinalysis to obtain microscopic hematuria. Several questions are essential when this scenario exists. First, where has the patient been treated for his/her previous stones (typical response is out of state, or they just moved to this area)? Were the stones obtained and analyzed? Some fictitious stone formers go so far as to present you with fake stones. There are many ways to evaluate and manage these patients. Initially, the number one pharmacologic therapy for colic worldwide is nonsteroidal anti-inflammatory medications such as toradol parenterally. If the patients are allergic to this drug, indomethacin suppositories should next be tried. The patients by this time are suspicious that you are not feeding them narcotics and often will sign out of the emergency department against medical advice. Even in contrast-allergic individuals, non-enhanced spiral CT has good sensitivity and specificity in the setting of acute ureteral colic. If unavailable, then a regular CT with overlapping cuts approximates the sensitivity of the spiral machines. Ultimately a diuretic radioisotope renal scan can rule out significant obstruction in those cases where lingering concerns exist. Even with spiral CT availability, the truly knowledgeable fictitious stone former can manipulate this situation. In a small series at the University of California, San Diego, two patients presented for narcotics successfully who had pelvic phleboliths that appeared like stones. These well-informed patients even had the knowledge that these calcified pelvic venous valves could cause false-positive CT scans [69].

One suggested and supposedly widely attempted method to handle fictitious patients was to identify them and generate a list of offenders. These types of files are actually allowed by the Health Insurance Portability and Accountability Act of 1996 (HIPPA), by JCAHO, and by various state regulations. Information though should be limited to what is necessary to diagnose and treating the patients. In one recent review, files were called "*frequent flyer file, repeater log, kook-book, problem patient file, patient alert list, and special needs file*" [70]. All of these can be taken to be disparaging and legal recommendation suggested the term "*Habitual patient files*" [70]. One other author advised about the risks of keeping such lists, though they are undoubtedly helpful. They advised keeping tight controls of such lists and advised taking a hard line with the drug seekers to discourage their returning to the emergency department [71]. Identify these patients and recommend intervention is the current recommendation. True drug users and addicts should be identified so they can be given help. Some patients are very demanding and place a strain upon the compassionate care and management and can be very manipulative. The physician can always compassionately refuse to give such patients narcotic pain medications. There are always alternatives such as per rectal indomethacin suppositories that are exceedingly effective for the pain of colic. Also methadone and long-acting morphine are also other choices because these are less likely to reinforce the drug-seeking behavior [72].

Discussion

Osler passed numerous stones during his lifetime, but only one while still at the Johns Hopkins University. This occurred after the publication of his textbook. This story of his first bout with colic is preserved in one of his resident's case reports reprinted in the Archives of Internal Medicine, in 1949. His subsequent musings on stone passage occur in his later career while he was the Regius Professor of Medicine at Oxford. He suspected that his stones were made up of uric acid. His autopsy is significant for noting "pinpoints of urates" studding his kidneys [18]. In his "*Principles*" a half of one lifetime previously, Osler can be quoted on the clinical varieties of calculi. He states that uric acid stones are "*by far the most important*." He might be predicting his own affliction in suffering from these recurrences and most certainly was aware of the risks of narcotics in his personal dealings with Halsted.

In one of the oddest textbooks of urology that has ever been published, one must rank Wirt Bradley Dakin *Urological Oddities* as one of the most peculiar [73]. He begins this publication in Preface as follows: "*The purpose of this volume is to present my entire collection of unusual case*

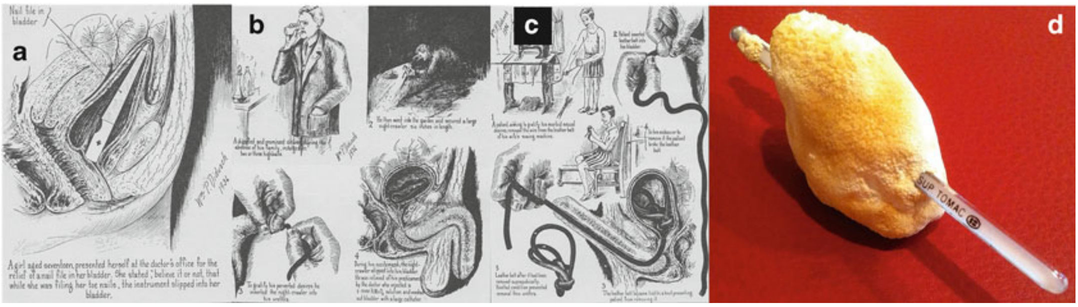

Fig. 22.1 Foreign bodies in the bladder. (**a**) Nail file in female bladder. (**b**) Earthworm in male bladder. (**c**) 3 ft of leather belt and wire tied nicely in a knot. (**d**) Excalibur

reports as a medical reference book leavened with occasional humorous anecedotes" [73]. That is the nature of urology, dealing with the urinary tract where the common excretory channel is tied intimately with the sexual organs leads to bit of the macabre. He alerts the reader "*All of this material was generously contributed by surgeons and physicians from nearly every country in the world for a period of fifteen years*" [73]. This would certainly indicate the magnitude of this problem since it is really a snapshot of only a brief period of time and that it is not isolated to one nation or culture. It is a splendid time to recall Giovanni Morgagni's famous case of the 14-year-old country girl. He presents this case in Book III, letter XLII, article 20, with one of the first descriptions of stone formation upon a foreign body: "*a country girl…died in her fourteenth year. For having introc'd a brass hair-bodkin, notwithstanding it was bent in the middle, very high into the urethra,…she was silent as to the true cause of the pains. For even the bodkin could not be extracted, by reason of a calculus that was form'd upon it. But the ureters, and the kidnies themselves, were in a very bad condition indeed*" [74]. Dakin begins chapter four ominously with his title, *Foreign Bodies in the Bladder, Autoeroticism* [73]. An auspicious beginning but he will go on for 67 more pages of one odd case after another gathered from throughout mainly North America. He then presents 212 cases or vignettes of these oddities with the urinary bladder [73].

Let's summarize this rather extensive collection of predominately, though not entirely self-inflicted, bladder foreign bodies. New York State was the most represented populace in this bizarre collection of bladder foreign bodies, beating out California 28 cases to 23. There were 35 states represented showing a broad area of those afflicted with the desire to insert things into themselves, plus the District of Columbia. Cases from Canada were also included ($n=10$) as well as several from England ($n=10$, all from London) and a solitary case from New Zealand. There were 111 identified male subjects, 61 females, and only 40 where the gender was not indicated. Every ethnicity was noted except the Inuits or Eskimos (but 3 Native Americans were included). Ages ranged from 4-year-olds to 76. After much anticipation it is time to move on to the *objects du jour*. Chewing gum apparently is or was the most common inserted item, no mention of flavors though "spearmint" odors were commonly mentioned ($n=22$). Bobby pins or hairpins (22 was the largest number extracted at once) were present in 18 cases, glass rods in 18, thermometers were noted in 11, slippery elm and sundried wood pieces in 12 (this is most likely attempting abortion but inserting the wood into the wrong orifice, slippery elm, was a common method of inducing abortion), and crayons and candles in 17 (very common for multiples; especially birthday candles). There were high rollers whom inserted two gold watch chains and one gold pessary stem placed into the bladders. Now we come to the more esoteric items; these are only single reported case: a nail file (Fig. 22.1a), squirrel's tail, squirrel's penis, earthworm (Fig. 22.1b), snake (without head), hog's penis, two snails, a windshield wiper blade, a French fry, 16 g. of carrots, a baby's rattle, and finally a fetal skeleton (probably eroded into the bladder). Then there are those paraphernalia that the volume of material inserted is itself exceptional as follows: a whole tureen of gravy (coagulated and crystallized but variety not mentioned), 24 in. of radio wire, 3-ft-long leather and metal belt (Fig. 22.1c), 18 ft of fishing line (the stone was the size of a baseball), 6 ft of 26 ga. wire, a three-foot shoelace, thirteen and a half feet of string, two balloons (uninflated), and a 6-mm 109.5-cm-long rubber tube [73].

Though Dakin was certainly not the first medical author to discuss the bizarre practice of introducing a foreign object into one's own urinary bladder, he certainly was the most graphic. In fact, the tradition that he started, particularly in the American West, has continued during the Annual Meetings of the Western Section and of the American Urological Associations as the Round Table Forum. That this goes on still is exemplified by the case of Excalibur, recently removed stone with thermometer. It was of course an accident (Fig. 22.1d).

It is fitting to close this atypical historical section with Sir William Osler's greatest fictitious creation Dr. Egerton Yorrick Davis [75]. Bean who was one of Osler's disciples noted also that "*An erratic spirit made him a perennial practical joker, provided a vehicle for his unquenchable ribaldry, and supplied many a nagging, and not completely answered, question in our efforts to evaluate the whole man*" [75]. Egerton Yorrick Davis was Osler's *Nom-de-plume*. He launched this factotum in 1882 entitled *Professional notes among the Indian Tribes about Gt. Slave Lake, N.W.T.* by Egerton Y. Davis, M.D. Late US Army Surgeon that he submitted to the Canada Medical and Surgical Journal. He pulled this back and it sits now in the Osler Archives at McGill University [76]. He hit the big time however with his now memorable "*Vaginismus*" published on December 13, 1884, in the *Medical News* [77]. Davis describes a fictitious "case of '*De cohesion in coitu*'." His third major contribution was on March 6, 1886, when he penned *Extrauterine pregnancy changed to intrauterine pregnancy by electricity* [78]. This starts off so typically Oslerian that it deserves repeating, "*Sir: In this age of ohms, amperes, and volts, skepticism as to the power of electricity is in the highest degree unreasonable- not to say reprehensible. If electricity, transported thirty-five miles by telegraph wire, can move an ordinary locomotive engine from one place to another, surely the same power can cause an embryo to move a few inches along the* ***Chemin de Fallopius!***" [78]. Osler certainly was closing ranks with tall tales of Baron von Munchausen. There is so much more that sadly cannot be included here, but the author is passing a stone currently and is running in for a quick pick-me-up of morphine at the local spa [76].

One final postscript in the legend of E.Y.D. will fittingly end this chapter. In 1896, the incomparable Johns Hopkins artist Max Brödel made a small cartoon captioned as "*The Saint-Johns Hopkins Hospital*" (Fig. 22.2). He endorsed this by hand with the following: "*For this scandalous*

Fig. 22.2 Saint-Johns Hopkins (Max Brödel)

canonization- with the consent and affirmation of Cardinal Gibbons- Max Broedel [sic] is responsible. E.Y.D [79].

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wording to the first, which was presumably a practice session."
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23 Early Modern Stone Disease

Introduction

> "*The philosophies of one age have become the absurdities of the next, and the foolishness of yesterday has become the wisdom of tomorrow; through long ages which were slowly learning what we are hurrying to forget, amid all the changes and chances of twenty-five centuries, the profession has never lacked men who have lived up to the Greek ideals*." [1]
>
> —Sir William Osler

At the outset of the twentieth century, stone gods walked the face of the Earth and stone disease trembled. Though metaphorical, these concepts were somewhat close to reality. Stone disease clearly represented a complex group of disease processes that resulted in a common manifestation that is the development of concretions within the urinary tract. The underlying pathophysiology of the varying causes of the disease was beginning to be unraveled. The causes of pain, the treatment of pain, and the associated nausea and vomiting were all falling. Prevention was not yet possible, but clearly the causes were becoming known and at actual scientific investigation into preventative strategies were being tried. In Baltimore, an experiment in medicine was taking place, the rise of a new type of medical school. In addition, we have outstanding records from this era, and H.L. Mencken, considered the sage of Baltimore, was present throughout the early days of Johns Hopkins: "*The goods that a writer produces can never be impersonal; his character gets into them as certainly as it gets into the work of any other creative artist, and he must be prepared to endure investigation of it, and speculation upon it, and even gossip about it*" [2]. Menken was unique because he was intelligent and occupied a ringside seat to Hopkins's formative years [3]. Menken was not shy in his thoughts or feelings: "*Halsted stood clearly at the head of the list, with Osler a good distance below him. Probably on a level with Osler stood Kelly; then there was another drop to Welch*" [3]. We have already presented Sir William Osler's advice regarding urolithiasis from his *Principles and Practice of Medicine*. Now it is time to move to another of Hopkins's founding faculty.

Howard Kelly was one of the Johns Hopkins professors immortalized in the John Singer Sargent's painting called *The Four Doctors* (Fig. 23.1a) [4]. Kelly was one of the four fates, immortalized with his fellows: Osler, Welch, and Halsted. Kelly was interested in gynecology, but a far cry from our modern notion of today, he was interested in much of the diseases of women, including urolithiasis [5]. Howard Atwood Kelly was born on February 20, 1858, in Camden, New Jersey. He attended medical school at the University of Pennsylvania and fell under the spell of the young internist, William Osler. He was an associate professor of gynecology when he met Osler, and he moved to Johns Hopkins at the age of 31, 1 year after Osler was installed as physician in chief [5]. He was interested in developing new surgical techniques and developed his own cystoscope; he first utilized absorbable sutures on the GYN service at Hopkins.

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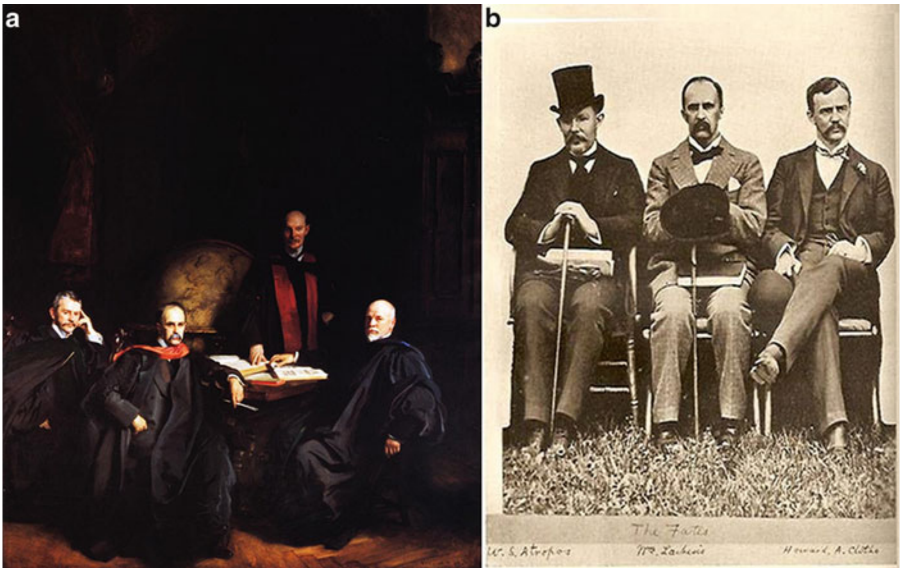

Fig. 23.1 (**a**) John Singer Sargent's famous painting of the four professors of Johns Hopkins School of Medicine (The Four Doctors). (**b**) The three fates of Johns Hopkins (W.S. Atropos, Wm. Lachesis, and Howard A. Clotho)

He was a gifted technical surgeon by all accounts. He read Hebrew, Greek, and Latin, in addition to German and French, and was attracted to seminal works in the evolution of medical thinking. With Osler, William Henry Welch, and others of the Hopkins faculty, he founded the Johns Hopkins Hospital Historical Society. He published Cyclopedia of American Medical Biography (1912), which contained biographical essays on about 1,100 eminent deceased physicians and surgeons from 1610 to 1910; Some American Medical Botanists (1914); American Medical Biographies, with Walter L. Burrage (1920); and Dictionary of American Medical Biography, with Burrage (1928). He was an amateur herpetologist, and exotic snakes could be found roaming about his house along with his nine children [5].

Kelly was substantially interested in urolithiasis. In his textbook entitled Diseases of the Kidneys, Ureters and Bladder, he begins [6]. He begins his Chap. 20 on renal and ureteral stones with some history. As he is a classics scholar himself, this is poignant. He mentions that Scrapion, a Damascus physician of the ninth century, mentions surgery for kidney stones. He notes that Riolan, the anatomist, noted that stones are present in the pelvis and the kidney. Riolan describes what he calls "coral stones" and might benefit from surgery in 1649. He describes the experimental findings of Zambeccari in the "*Nova Acta Eruditorum*" where he performed nephrotomies in dogs in 1670. He describes the pathology of kidneys of patients with stones from Nicolaes Tulp whom Rembrandt immortalized [6]. We've encountered his colleague's comments on urolithiasis, William Osler. Now let's turn to some of Kelly's thoughts, "*No stretch of chemical or physiologic imagination will permit so heterogeneous a group of compounds to be ascribed to a common origin or their deposition, in the kidney, ureter or bladder to be uniformly charged to an identical cause*" [7]. We will return to Kelly again in the section on surgery, because he has one substantial contribution along with his favorite artist/illustrator Max Brödel.

Hugh Hampton Young (1870–1945) certainly was not one of the founding fathers at Johns Hopkins Medical School but he was one of the early surgical residents with William Stewart Halsted, whom we've already met [8]. Many consider Hugh Young to be the father of American urology, since he became the first head of urology at the Johns Hopkins Hospital and the founder of the Brady Urological Institute which combined patient care, house staff education, and research in one building [9]. Young was born on September 18, 1870, in San Antonio, Texas, to a former Confederate Army general. His grandfather was a physician and surgeon in Charlottesville, VA, and Hugh went to the University of Virginia for college and medical school, receiving his M.D. in 1894. He decided upon a career in surgery and went to Johns Hopkins in 1894, but there were no positions available to him. He decided to stay even though no job was available and fortune smiled upon him; during the holidays, Dr. J.M.T. Finney needed help and Young was available to begin helping the young junior surgeon. Young became his assistant and began to give anesthesia while doing research in microbiology. He began to work for Dr. James Brown to study bladder dysfunction when Brown suddenly died, therefore leaving Young with no supervising physician. In October of 1897, Young recounts that he was rushing down a hospital corridor and literally ran into Dr. Halsted as he rounded a corner. Young was always in awe of the "*professor*" and was profusely apologizing when Halsted retorted, "*Don't apologize, Young, I was looking for you to tell you we want you to take charge of the department of genitourinary surgery*" [8]. On November 29, 1897, at the age of 27 Young became in charge of the dispensary of genitourinary diseases. Young would develop many innovations in urology, one of the first genitourinary disease operating tables that could use X-rays in the operating room to identify stones. He designed urologic instruments, first used mercurochrome, was one of the founders of the American Urological Association, and was the founding editor of the Journal of Urology in February of 1917. He wrote the forward to the first issue and the second paper in the founding volume on "Double ureter and kidney, with calculous pyelonephrosis of one half: cure by resection" [10]. His most significant legacy might have been his own house staff who went on to populate many more urologic training institutions, including Alexander Randall. It is recorded at Hopkins that Young wrote a quick note to his formal pupil, Randall, as follows: "*Drop me a line soon and give me the latest dope on the solution of calculi by vitamins and special diets*" (dated February 28, 1935).

An Indian Rhinoceros

The famous male Indian rhinoceros, *Rhinoceros unicornis,* was purchased for the London Zoological Society in 1834. When the unfortunate animal died, Richard Owen, the famous physician/anatomist, was called to perform a dissection of the rare animal. Owen, the Hunterian professor of comparative anatomy, discovered during the dissection a small group of glands on the thyroid of the rhino [11]. He noted, "*The thyroid gland consisted of two elongate, subtriangular lobes extending from the sides of the larynx to the fourth tracheal ring… The structure of this body is more distinctly lobular than is usually seen; a small compact yellow glandular body was attached to the thyroid at the point where the veins emerge*" [12]. As is so often the case in science, another was poised to discover the same gland; this time Ivar Sandström who was a medical student in Sweden found it in the dog. He also looked at the rabbit, the cat, and a horse to confirm his findings. He published his *On a new gland in man and several mammals* in 1880 and was originally given credit until Owen's report was rediscovered by his successor, A.J.E. Cave [13].

The Hunterian curator certainly was aware of Owen's discovery. S. G. Shattock who we've discussed in a previous chapter also quoted Owen's paper in a 1905 work *The parathyroids in Graves's Disease* [14]. Others also had noted the small yellow glands including Remak in 1855 and Virchow in 1863 [11]. Owen's star was descending as his nemesis and chief opponent Thomas Henry Huxley's was rising (along with his hero Charles Darwin). Now the link towards the development of urolithiasis and the association with bone resorption was possible. These links would forge the beginnings of systematic investigations into the complex physical chemistry of urine and the development of models that would clarify the various methods for all our current notions of how stones arise.

We have sampled briefly some of the very early Johns Hopkins contributions to stone disease and can easily appreciate how a nucleus of intelligent and committed individuals at one center can accomplish great things. Now it is time to move a second center that also arose in the early twentieth century to contribute greatly to our knowledge of stone disease and to what is now called "mineral metabolism." This is the Harvard Medical School and the Massachusetts General Hospital in particular. Fuller Albright was born in Buffalo, New York, on January 12, 1900. He grew up a sportsman and loved fly fishing, especially fond of Wilmurt Lake in the Adirondacks. He entered Harvard but was side tracked by World War I and he contracted the Great Influenza but was a survivor. He returned and finished medical school at Harvard and elected to Alpha Omega Alpha. He became friends with Read Ellsworth and they both were mentored by Dr. Joseph Aub from endocrinology and basic research. Albright and Ellsworth would continue to collaborate for another 16 years until the latter died of tuberculosis. Between 1928 and 1929 Albright went to Vienna to study with Dr. Jacob Erdheim who established the relationship between the parathyroid glands and the calcium metabolism. Albright would later say of Erdheim, "*quite simply he knew more about human disease than any other living man*" [15]. Albright returned to the Mass General and began a research unit called Ward 4, which is a 10-bed research unit (shades of Richard Bright) [16]. He staffed the Stone Clinic every Wednesday (nicknamed the Quarry) with a team that included urologists; we've already met Suby in a previous chapter [17]. Some of the stone patients would make it to the experimental ward. Beginning in the 1920s and through the mid-1930s, Albright primarily focused upon the dietary effects of calcium and phosphate balance in normal subjects, hyperparathyroid patients, and hypoparathyroid patients. In 1934 he published a report on 17 patients who had undergone surgery, the largest series of the time [18]. Albright married Claire Birge in 1932 and they had two sons [15]. In 1937 he suggested that parathyroid hyperplasia was secondary to phosphate retention in patients with renal failure [19]. Albright contracted progressive Parkinson's disease perhaps secondary to the influenza, and he could no longer write by the 1940s and could hardly speak by the 1950s [15]. Yet during this time, Albright and his team discovered nephrocalcinosis associated with renal tubular acidosis in 1946 [20]. In 1949 he noted stone disease associated with the milk alkali syndrome [21]. Finally in 1953 he presented on 35 patients with idiopathic hypercalciuria, hypophosphatemia, and normal serum calcium [22].

Fuller Albright contributed to other areas of mineral metabolism and to medicine in general. In 1944 he was president of the American Society for Clinical Investigation and gave a memorable address [23]. He developed a quaint diagram called "*The Road Leading to the Castle of Success*" [23]. He admonished the clinical investigator to not get swamped with patients (not so doable any longer), not to get segregated entirely from the bedside (see patients), and to read widely [23]. These could almost be paraphrases from one of Osler's sermons. Fuller Albright underwent a controversial operation in 1956 for control of his Parkinson's disease; he initially did well from the first procedure but developed an intracranial hemorrhage during surgery on the contralateral side, and he remained in a persistent vegetative state for 13 years. He died on December 8, 1969, and was cremated with his ashes spread upon Wilmurt Lake [15].

Alexander Randall

Alexander Randall was a gifted physician who became a young urology resident at the new program at Johns Hopkins University. He did basic research in urolithiasis while at Hopkins and continued his interests at the University of Pennsylvania where he spent the bulk of his career. Randall was born on November 18, 1883, in Annapolis, Maryland. He was the only son to J. W. Randall, an attorney, but he had three sisters. He grew up on the bay, learning to sail, and his first scientific expedition at the age of 20 was a cruise with the Bahamas Expedition for 3 months prior to medical school. He was a "classics" major and entered the John Hopkins Medical School graduating in 1907 [24]. He went into medical practice in Philadelphia where he fell under the influence of John B. Deaver who was interested in genitourinary problems. In fact, Deaver influenced a whole group of young physicians who all became urologists. Randall returned to Hopkins to work with the young professor of urology, Dr. Young. From 1910 till 1912 Randall was one of Young's first protégés prior to his returning to Philadelphia where he spent the remainder of his career [25]. In 1929 Randall was promoted to associate professor at the University of Pennsylvania and he was the director of the residency training program since 1923. He introduced intravenous pyelography in the USA after von Lichtenberg came as a visiting professor in 1937 [26]. He published in 1931 his magnum opus, Surgical Pathology of Prostatic Obstruction which made him famous. This dealt with careful autopsy findings of 1,218 patients to evaluate the effect of the prostate on the bladder [27]. He also became the president of the American Urological Association in 1931 and a founding member of the American Board of Urology in 1935 [28]. In his presidential address we can again see the influence of his time at Johns Hopkins for he quotes William Osler several times and concludes in the classic Oslerian fashion by quoting a poem from McCrae [28]. In 1936 he began to present his experimental work on urolithiasis that will form the basis of the rest of the comments in this chapter on Randall.

On the evening of November 14, 1935, Alexander Randall was invited to present his newest research on urolithiasis to the New England branch of the American Urological Association's meeting in Boston [29]. This was an auspicious beginning of the work that has captured the interest of many modern research centers today. In the audience was Fuller Albright from the Mass General. Randall began, "*When one undertakes to explain the origin of stone in the upper urinary tract, one appears to be confronted by the fact that our theories of today seem to be increasing the complications of the picture rather than its simplification*" [29]. He then goes on in some detail to discuss the five major theories "relative to the causation of renal calculus." It is simpler because of Randall's tendency to be somewhat loquacious to list the five as follows:

1. Dietary theory—two parts to this, first a deficiency (childhood stones), vitamin A deficiency
2. Infectious theory
3. Urinary stasis
4. Disturbance of colloidal mechanisms
5. Hyperparathyroidism (did he know that Albright was going to be present?) [29]

He then warmed to his evening's agenda the introduction of his new hypothesis: "*There seems to be a broad gap between the theoretical mechanism for possible stone growth in the renal pelvis, and our accurate knowledge as to why a stone came into existence*" [29]. He followed with the quip, "*We seem to have a plethora of theories and a paucity of facts*" [29]. He then gave three arguments that there was still something missing in all of these theories, though he argued that each of the five categories had significant overlap with each other. His first was that none of the five explain asymptomatic crystalluria; the second was that stones are often unilateral and none of the five explained this, and third was that no one of the five theories was infallible and could not explain all cases. Here he discussed his experiments for 3 years that served to explain the causative factor in the five theories that he had failed to find the cause of stone formation: "*Let me present this hypothesis in very brief form. I believe there are but two basic causal factors which are capable of initiating the development of a stone in a renal pelvis*." He then presented both of his ideas, "*In the first class, or the 'primary' renal calculi, one finds those cases in which the clinical picture is especially clear, and every physician…such a calculus has arisen as a gradual crystallization upon a lesion in the renal pelvis*" [29]. This was what is now known as Randall's plaques. I want to give another of his comments, because Randall was historically minded as we will specifically see in the very next chapter, but he states, "*You cannot find in the textbooks on pathology of today any mention of any pathologic condition occurring in the renal pelvis, other than the generalized one of pyelitis*

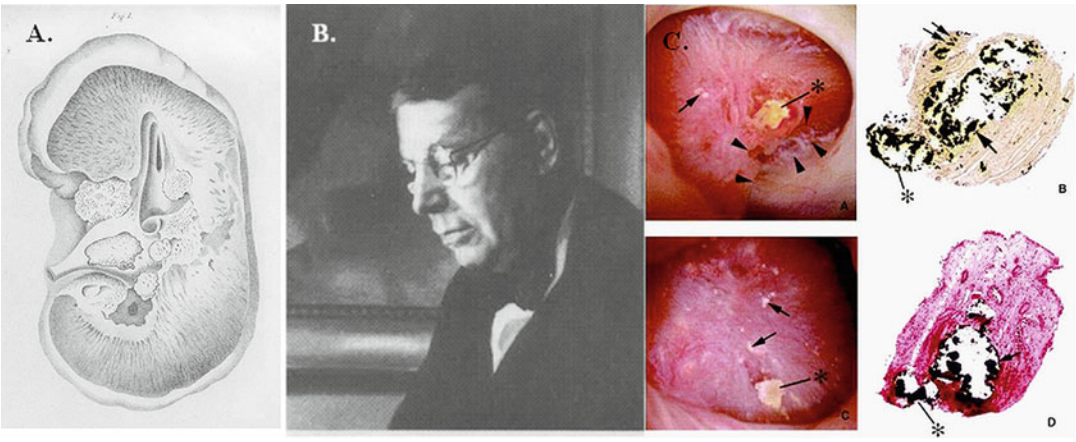

Fig. 23.2 (**a**) John Green Crosse's 1833 depiction of papillary concretions forming in a kidney, (**b**) Alexander Randall, C. Randall's plaques with stone formation

or the very self-evident of tumor" [29]. As we have already documented in some detail in previous chapters that this was certainly not the case. Morgagni suspected deposits were occurring in tubules as did others. The most telling evidence of speculations like his are Crosse's with even an illustration of papillary calcifications in 1833 (Fig. 23.2a) [30]. Henle in 1862 noted "*calcium infarcts*" in the renal substance and tubules filled with chalk [31]. Also Beer reported in 1904 in a study of 100 kidneys that deposits of lime in 53 % but never in a kidney in a person under 24 years of age [32]. Finally, right before he started his research, Huggins also clearly described calcifications and papillary lesions in a large American series of nephrectomies performed for nephrolithiasis, similar to Crosse's observations [33]. Now to his second hypothesis, "*In the second class belong the calculi which form in a renal pelvis in which urinary stasis present because of some obstruction to the normal urine flow*." He then moved on to his discussion where he talked about the 3 years of laboratory work that led up to this report and introduced his future work that will include more cadaver studies.

The whole discussion was recorded in the publication that followed. Dr. Fuller Albright was present and his comments are fortuitously recorded for posterity. Though his full remarks are too lengthy to present here, we will again take key points for our consideration. He begins by telling why he is at this urology meeting, "*I am very much indebted to this society for inviting me here tonight and giving me the opportunity of hearing this very interesting presentation*" [29]. Of all the responses recorded, Albright's would be the only skeptical one, and his response was fascinating. He begins by updating his work on hyperparathyroid patients, now 29 in number, and 19 have urolithiasis affecting 23 kidneys. He expressed doubt that Randall's observations were the primary causative factor, since stone patients have abnormal excretion of both calcium and phosphate which is the primary causative factor. He stated emphatically, "*We believe more and more the theory that increased crystalloids in the urine are the primary factor in most cases of stone formation*" [29]. He pointed out that he had no information on how the actual stone gets started, like Randall was proposing, but this would not occur if the urine was not supersaturated to begin with, thus starting the problems that Randall's hypothesis would ultimately encounter until our modern era. This is the age-old argument of what is the "*initiating event*" that even goes on in modern particle physics debates—what are the primary particles or can we keep subdividing them forever? Randall of course did not sit idly once these comments were expressed; he responded, "*I have been especially* *interested in Dr. Albright's work, but he answers his own question, for I do not mind if the tubules are congested with precipitated salts, they must come out from the tubules on the papilla, causing trophic changes and further crystallization*" [29]. He did find Albright's Achilles' heel however with his next comment but failed to address the real point of Albright's, that the supersaturation must be present initially, but let's continue the drama with Randall's response: "*Of course, his picture is on one side only, that of calcium phosphate, and it doesn't enter into the picture one iota if uric acid calculi are present*" [29]. As it turns out, they were probably both correct but in just a matter of definition they might have missed the central issue; defining what is the precipitating event or the metaphor of the chicken and the egg applies as supersaturation drives crystallization either in the interstitium (subendothelially for Randall) or in the collecting ducts (type II Randall's plaques) and subsequently forming on the exposed plaque (type I Randall's plaque).

For the next 5 years, Alexander Randall presented paper after paper on this topic, using almost the same arguments that he deployed in mid-November 1935. He added a wealth of data on cadaveric kidneys. On March 1, 1937, he presented a paper he had presented at the Annual Oration of the Philadelphia Academy of Surgery followed by a second at the American Association of Genitourinary Surgeons in Stockbridge, MA. These papers were entitled *The origin and growth of renal calculi* [34] and "*The initiating lesions of renal calculi*" [35]. He again presented the five theories that echoed his talk in Boston. He asserted, "*Therefore, in offering a hypothesis for the origin of stone, these two postulates were formulated and they have presented the basis for a series of research problems in an effort to prove or disprove their accuracy: first, that an initiating lesion had to exist; second, that any such lesion should be sought for on the renal papillae, or close thereto*" [34]. He then looked at autopsy studies on the kidneys in 104 patients. He found small intrarenal stones in 12 and postulated a four-stage process of stone formation. Step one was a "*deposit of calcium, entirely devoid of any inflammatory evidences, as being laid down in the wall of the renal papilla…entirely below the surface of the cells covering the papilla*" [35]. He noted the second stage "*the characteristic 'milk patch' deposit, but on the surface of one such 'milk patch' could be seen a tiny black dot*" [35]. Stage three followed, enlargement of the still-attached stone. The fourth stage was release from the point of attachment of the calculus. He used a particular pathologic specimen to illustrate each of these stages. This was deposition of renal solute forming the first appearance of the urinary stone (Fig. 23.2c). He looked at removed human stones to further augment the attachment ideas and location of the nucleus within the stones [36]. His interest in stones continued for several more years; he published two studies in 1940. In these he updated his findings on 1,154 autopsies and presented more of the pathologic data. These points of origin were sterile, usually noninflammatory, and the nidus was typically calcium phosphate. The incidence of plaques was 19.6 % and increased with age, peaking in between 60 and 69 (at 29 %). He concluded with the following comment, "*These facts carry definite proof of the papillary origin of a primary renal calculus…*" [37, 38].

Randall's health began to suffer during this period [24]. Ironically in 1937 Randall was treated with high doses of sulfathiazole, poorly soluble in the urine and might have caused acute renal toxicity and sulfa stones with crystalluria [39]. His blood pressure rose though his renal function apparently improved [40]. He had a minor stroke in 1941 and eventually suffered from a series of strokes that eventually led to his death on November 18, 1951 (Fig. 23.2b). His work did eventually lead others to take up the investigation of plaques, but serendipitously it was the thoughts of Albright that would trump the findings of Randall for about 20 years. Supersaturation theories had the backing of the basic scientists in crystal chemistry and physics. Randall's notions though would not pass away quietly in the night, and we will follow this trail in the rest of this chapter. Randall did have one further contribution that we will discuss later in the chapter on The Largest Stone of All.

Baby Steps

It didn't take long for the negative aspects of Randall's observations to begin to unravel. That is not to say that Randall's observations and speculations were not championed by others, for those who believed in the Randall hypothesis would not go away. We have seen that Albright was not convinced in the primacy of Randall's plaques. Two other early American investigators also became unwitting antagonists to Randall's theories. First was Charles C. Higgins whose studies on vitamin A-deficient rats and the formation of calcium phosphate urolithiasis did not include plaque formation [41]. Higgins was an investigator at the new Cleveland Clinic, and he would continue his studies and reported upon the resolution of stone disease in humans by supplementing vitamin A (cod liver oil) and the use of an acid ash diet [42]. It was Higgins's studies that prompted the letter of Hugh Young to Alexander Randall. Next was Linwood D. Keyser from the Mayo Clinic who began experimenting on animals following up the theories of Minkowski and Ebstein from Germany [43]. He also observed that stones formed more like the process outlined by Albright that favored the supersaturation theories, except that Keyser did more detailed crystallographic methods that supported the theories of Rainey, Ord, and Henry Vandyke Carter's observations on the inhibitory properties of urinary proteins [44]. It is interesting that others at the Mayo were also not aware or not interested in the aforementioned papillary concretions [45]. Finally, Kjølhede and Lassen likewise found caliceal stones in 14 patients, and in six cases, there was no associated Randall's plaque suggesting no association with stone formation [46].

Early support for Randall's hypothesis came from Posey who found radiographic plaques in 35.7 % of his cases; however, he noted that only 6 % of these patients had symptomatic stone disease [47]. Vermooten was another advocate who also noted these lesions commonly in stone formers [48]. He went on to quantify at autopsy of South Africans that plaques were present in 55 % of healthy people and 45 % of hospitalized patients. He noted that 17.2 % of Caucasians had plaques versus only 4.3 % of Bantu natives [49].

Leo Anderson and John R. McDonald entered the "stone origins" controversy, suggesting that there is even an earlier identifiable lesion prior to the overt demonstration of Randall's plaques [50]. The "initiating lesion" was demonstrated in 148 surgically removed kidneys and 20 apparently normal autopsy kidneys. They found tiny microscopic calcareous lesions in the pyramids of almost all kidneys. The only groups free of such lesions were children under the age of two. Anderson developed two postulates of his own for his findings: First, the concentration of calcium and related ions is high in the tissue and fluids about the renal tubules. Second, he suggested that phagocytic cells ingested microscopic crystalline debris and removed this substance into the lymphatics [51]. Historically, Anderson was much more thorough than Alexander Randall in quoting the history of papillary calcifications, noting the work of Randall, Vermooten, Henle, Beer, and Huggins.

Reginald J. Carr was next on the historical pathway started by Randall. Carr was a radiologist who was interested in the X-rays of kidneys, especially in stone formers.

Carr examined by sophisticated radiologic techniques about 98 partial nephrectomy specimens and 111 autopsy kidneys that have no documented history of stone disease. He made thin slices of the renal tissues and really high definition radiographs. He noted concretions in three locations within the renal papillary regions. First, just outside of caliceal fornix regions or at the sides of the renal pyramids, he noted calcifications. Next he noted calcifications in the corticomedullary junction zone. Finally he noted them immediately beneath the renal capsule [52]. The surgeon who performed the partial nephrectomies, described as a "radical cure" for stone disease, was H.H. Stewart [53]. Carr even began to use the terms Stewart's nests and Carr's pouches for the specific forniceal regions where these concretions were commonly found [54]. Carr had the insight to utilize other experimental works of Willard Goodwin and Joseph Kaufman on the anatomy of the renal lymphatics [55]. He summarizes, "*We known that in the lungs particulate matter inhaled gets into the alveoli, and then it is taken* *up in the lymphatics and transported to where it can do no more harm, as long as the mechanism is working properly. I believe that the kidney functions in the same way. I think that effete cells, debris of all sorts, calcium which has been re-absorbed and come out of solution in the interstitial fluid where there is always debris available to act as a nucleus to precipitation all get removed with the protein and interstitial fluid into the lymphatics*" [55]. Carr lauded Randall and his powers of observation and thinking and generally affirmed his suggestions. In 1979 André Bruwer put all of the information from Randall, Carr, and Anderson together in one continuum calling it the Anderson–Carr–Randall progression [56].

Carr however was not quite finished with his investigations of urolithiasis and their origins [57]. He discussed the radial striations we've already noted and investigated by others in previous chapters. He added X-ray diffraction and investigated the effects of "*organic matrix*." He noted that radial striation was always associated with concentric lamination, but the reverse was not the case. He demonstrated that the arrangement of minute crystals which form the calculus made up the radial striations. He also noted that calculi composed of calcium oxalate monohydrate had the radial striation oriented in a particular direction which was the "*b*" crystallographic axis; in cases composed of calcium acid phosphate dihydrate, it was in the "*a*" crystallographic axis [57]. Physical chemistry and crystal science applied to clinical stone formation. The organic component of stones was necessary for the development as it allowed diffusion of ionic groups but prevented disturbances in the process of crystallization, thus permitting growth to occur. The organic matrix was therefore continuously incorporated into the stones composition (shades of Rainey and Keyser and the harbinger of William Boyce).

Rise of Modern Surgery

As the medical side of stone disease advanced at the dawn of the twentieth century, so too did surgical intervention. Spurred on by some of the greatest developments in the history of medicine itself, some believed that the late nineteenth and early twentieth centuries mark the high point of surgical science. Let's begin with the founder of aseptic surgery, Baron Joseph Lister (1827–1912). He was born on April 5, 1827, to a well-off Quaker family, and his father was the famous Joseph Jackson Lister who invented the compound microscope and achromatic lenses that aided another brilliant Quaker physician Thomas Hodgkin's work in pathology [58]. He attended the University of London and graduated with honors as Bachelor of Medicine and entered the Royal College of Surgeons at age 26. He moved to the University of Edinburgh to work with James Syme and eventually married Syme's eldest daughter Agnes who became his chief research assistant. He moved to the University of Glasgow as professor of surgery [59]. He had read Louis Pasteur's work on microbes and investigated the use of carbolic acid to reduce the infection rates of wounds. As a young surgeon he was distressed by his high rate of postoperative infections. "Hospitalism" had been coined to describe the widespread belief that being in an institution often was associated with bad outcomes [60]. In August 1865 he applied carbolic acid-soaked dressings to a compound fracture on an 11-year-old boy who survived, and his leg healed without needing an amputation [61]: "*But when it had been shown by the researches of Pasteur that the septic property of the atmosphere depended, not on the oxygen or any gaseous constituent, but on minute organisms suspended in it, which owed their energy to their vitality, it occurred to me that decomposition in the injured part might be avoided without excluding the air, by applying as a dressing some material capable of destroying the life of the floating particle*" [61]. Lister treated 11 patients with compound fractures during this period and nine recovered [62]. He began to be bolder; he started to treat all of his postoperative wounds with antiseptics. He treated bladder stones with suprapubic cystostomy and drained a perinephric psoas abscess all using his aseptic methods. In August 1867 at the Dublin meeting of the British Medical Association, he announced that during the last 9 months, "*his wards-previously amongst the* *unhealthiest in the whole surgical division of the Glasgow Royal Infirmary-had been entirely free from hospital sepsis*." He published a series of five articles in The Lancet from March through July of 1867 and was asked to return to Edinburgh in 1869 to take his friend and mentor's place [63]. Anecdotally, it is interesting that Lister while still a student in London was present in December 1846 when Robert Liston, a renowned surgeon for his speed, performed the first major surgery in Britain under ether anesthesia [59].

At about 8:15 on October 16, 1846, William Thomas Green Morton, an American dentist, arrived 15 min late for destiny. He had been hurriedly trying to collect his new glass inhaler from a local glassmaker. The surgeon, Dr. John Collins Warren, was waiting with thinly veiled pessimism for Morton to demonstrate inhalational anesthesia on his patient, Mr. Edward Gilbert, who had a neck tumor at the Bulfinch Building of the Massachusetts General Hospital. It was recorded that Warren had exclaimed, "*Dr. Morton has failed to appear and I presume he is otherwise engaged*" [64]. Morton arrived just in time and Dr. Warren noted, "*Well sir, your patient is ready*" [64]. With this Morton applied his mouthpiece to Mr. Gilbert and in about 3 min, first replied to Warren, "*Your patient is ready, Doctor*" [64]. After completing the operation, Warren said to the watching crowd, "*Gentlemen, this is no humbug*!" [64]. When Morton died at the age of 48 in 1868, Dr. Jacob Bigelow wrote his epitaph, "*William T.G. Morton, inventor and revealer of anesthetic inhalation, by whom pain in surgery was averted and annulled, before whom in all time surgery was agony, since whom science has control of pain*" [64]. Anesthesia was heralded as the "*greatest gift ever made to suffering humanity*" by the tabloids, but it engendered a raging controversy regarding precedence: "*The extraordinary controversy which has raged, and which re-rages every few years, on the question as to whom the world is indebted for the introduction of anesthesia, illustrates the absence of true historical perspective and a failure to realize just what priority means in the case of great discovery*" [65]. After Liston's first case, the People's Journal of London declared, "*Oh, what delight for every feeling heart to find the new year ushered in with the announcement of this noble discovery of the power to still these sense of pain, and veil the eye and memory from all the horrors of an operation…WE HAVE CONQUERED PAIN*" [64]. Other agents quickly followed, chloroform (1847); Sir Ivan Magill intubated the trachea; cyclopropane gas and sodium pentothal (Ralph Milton Waters of Madison, WI) was the next major advance, and no longer did the patient need to even be aware of the "gas mask" covering his or her face [66]. The alleviation of the pain of surgery allowed Lister to develop a safer approach to large bladder stones and removal of foreign bodies [67]. W.E. Henley penned in 1870 after having an amputation performed by Lister:

> "*Behold me waiting-waiting for the knife.*
> *A little while, and at a leap I storm*
> *The thick, sweet mystery of chloroform,*
> *The drunken dark, little death-in-life.*" [68]

Or perhaps more skeptically, George Bernard Shaw speculated, "*Chloroform has done a lot of mischief. It's enabled every fool to be a surgeon*" [69]. In one stroke, the necessity of speed over method had been eliminated.

Once more let's return to the hallowed halls of Johns Hopkins Hospital and look more closely as to why H.L. Menken would rate William Stewart Halsted so highly in this star-studded cast. Lister's methods took more of a circuitous pathway to success than did anesthesia. Though there were ardent supporters, there were also detractors, but a small group of young New York surgeons carefully began to adopt the aseptic technique in the SA; one of them was William Stewart Halsted (1852–1922). Halsted began to experiment on the novel local anesthetic agent, cocaine (first used by Freud), and he and his young colleagues all became addicted to this narcotic. Halsted's life changed profoundly; he went from an outgoing, charismatic young surgeon and outstanding instructor to a gruff, taciturn, isolated perfectionist [70]. Throughout this period he continued his brilliant researches in surgery and surgical techniques and he was supported by Osler and Welch [71]. His protégés literally changed the face of surgery; Harvey

Cushing became the father of neurosurgery and Hugh Young the father of American urology. Surgical training in the USA developed the scientific flavor of the German model; Billroth and Kocher were two great friends of Halsted other than his faithful dachshunds, Nip and Tuck [70]. Halsted literally transfigured our picture of the modern surgical arena. He introduced surgical gowns that were boiled and sterilized. Special caps were worn to keep bacteria from falling on the surgical field. He next introduced the sterile but reusable surgical rubber gloves that historically are linked to his scrub nurse, Miss Hampton, who later became Mrs. Halsted [71]. The picture of modern surgery was almost complete; only the masks were missing [72].

Ureterolithotomy

Surgery was now possible and stone disease was ready to undergo an epiphany. No longer was colic to be suffered and endured, when surgery offered a now painless and less risky method of delivering those suffering with stones. Aseptic surgery rapidly reduced the postoperative mortality and morbidity from wound infections. Upper tract disease could be diagnosed first with finely waxed catheters as demonstrated by Kelly, then increasingly with X-rays, and finally with intravenous pyelograms that could now accurately determine the size and location of the stone. But these massively successful methods did not all come at once. Many were the patients following the availability of both general anesthesia and aseptic surgical technique that would undergo surgery for an upper tract stone, with none being found. Aggressive surgeons were perhaps following the dictum of George Bernard Shaw.

In 1923, Herman Kretschmer summarized the knowledge of ureteral calculous disease into three distinct eras. First was the early time following X-ray introduction when patients were explored for presumed ureteral stones, and significant numbers of patients had none. Next, the era when ureteral catheters and retrograde pyelograms were done in suspected ureteral stone cases, but open exploration was again necessary with significant morbidity. He now describes the current trends of cystoscopic retrograde techniques [73]. Howard A. Kelly catheterized the ureters in most cases that he suspected a ureteral stone, even with good quality X-rays: "*It is our habit in catheterizing ureters in practically all cases to wax the catheter tip before its introduction. The wax on the end of the catheter serves the purpose of a tell-tale, revealing the presence of any stone encountered by it in its passage up the urinary tract*" [6]. He discusses the nuances of ureteral catheterization for stones: "*The catheter must be introduced into the ureter without touching the side of the speculum. Striking the metal makes a flat, smooth facet which cannot be mistaken for the gouge of the calculus*" [6]. Once withdrawn, the waxed catheter is taken and examined in bright light with a magnifying lens from 3 to 5 diameters, looking for the telltale scratches of a stone. Kirkendall described a method of adapting Kelly's technique of waxed catheter passage for catheterizing cystoscopes. He lined the outer sheath of the cystoscope with a loose-fitting rubber tube which protects the catheter during passage [74].

Winsbury White in his 1929 textbook *Stone in the Urinary Tract* devotes Chaps. 7–9 to the diagnosis and treatment of calculus in the ureter [75]. He notes the percentage of stones presenting at different levels of the ureter as follows: lumbar 22 %, iliac 7 %, pelvic 51 %, and intramural 17 %. He too did not depend solely upon the radiograph; he used Kelly's method of waxed catheter. He begins, "*There are three alternatives in dealing with a ureteric calculus: the stone may be left to pass by natural means, its passage may be aided by transcystoscopic measures, or it may be removed by operation*" [75]. In Young's magnum opus *Young's Practice of Urology, Based on a Study of 12,500 cases*, his table 48 in Volume II displays the outcomes from their 116 cases of stone disease [76]. Ureterolithotomy was performed in only six patients ("3 well, 1 improved, 1 dead, 2 no reply"). Kretschmer noted in 140 cases of ureteral stones, patients passed them spontaneously in 26 % of the time [73]. He also reported that stones 5 mm or less were the most likely to pass. Crowell presented a series of cystoscopic management of stones and reports on various methods of management. He used local anesthesia of 2–5 % procaine and injects the anesthetic up the ureter on impacted stones, occasionally injecting oil to get a catheter to slide by the stone. The catheters were tied in place and slowly exchanged for larger sizes daily until two no. 11's and one no. 6 are all in together [77]. Rapid dilation of the ureter was described by Bransford Lewis using metal dilators and bougies but noted a danger in pushing the stone back into the kidney. Bugbee recorded the success of cystoscopic treatment as 326 successes out of 347 cases, and Crowell noted 88 successes in 98 cases [78]. Contraindications to cystoscopic manipulation of ureteral stones were described as stone sizes above 2 cm., impacted or encysted stones, acute infection, and in cases where there is known disease in the bladder or prostate. Ravich reported on a personal series of 758 cases or ureteral stones in a private series. Only 48 patients passed their stones spontaneously, 456 passed the stone after simpler cystoscopic manipulations, 17 were advised to have surgery but refused, and 68 were required open surgery. His open surgical incidence was 11.2 % [79].

John Swift Joly also waxed eloquently on the management of ureteral stones in his chapter 6 of *Stone and Calculous Disease of the Urinary Organs* [80]. Joly presented the incidence of bilaterality of ureteral stones to be 3 % but thought it could actually be higher in silent cases that present only as postmortem cases. He worried about small stones as well as large ones, "*A large ureteric calculus simply means that the stone has not given rise to obstruction, and that the function of the kidney above it has been more or less preserved. This is only relative, as rapid growth of the stone indicates the presence of infection, and the kidney sooner or later succumbs to the infection*" [80]. Joly also discussed methods that have been used historically to try to induce ureteral stone passage. He noted that Albarran recommended significant hydration: "*Diuretics have been suggested including citrate of potash, diuretin, theocin sodium acetate, weak tea, barley water, Vittel and Contrexéville water (mineral waters)*" [80]. Belladonna was recommended by some, but questioned by Macht, and he describes the use of papaverine injected subcutaneously recommended by Bachrach [81]. Oral glycerin "*does not appear to have any definite action*."

Bumpus and Scholl reported on 640 cases of ureterolithotomy from the Mayo Clinic and had an operative mortality rate of 0.62 % [82]. They discussed the imperative of knowing at the time of exploration the exact location of the concretion for planning the surgical incision site. They recommended an X-ray within 1 day of the surgery. They recommend an extraperitoneal approach in all cases once the stone was palpated to secure it prior to incising the ureter to prevent it slipping retrograde back up the dilated ureter. Once removed they further recommended exploring the ureter with a bougie to insure that there are no further stones. They did not routinely suture the ureterotomy closed, stating that it is difficult to suture the ureter many times because of the inflammation. They recommended leaving a small drainage tube which is placed next to the ureter in the vicinity of the incision and generally removed after 48 h. Closing this discussion on ureterolithotomy with some comments by Frederic E.B. Foley, the inventor of the indwelling catheter, seems appropriate [83]. He began with the following comments, "*In recent years, ingenious devices and methods have been perfected for the passage or removal of ureteral stones without resort to operation*" [83]. You can almost anticipate at this point that he is going to decry the newer, less invasive therapies for a careful open alternative, like the naysayers to Civiale: "*There is much evidence that this attitude has carried too far and that the just purpose of such management is becoming subordinate to mere zeal for its use*" [83]. We can follow his path throughout the article, but he believes that the open surgery itself can be modified, making what was a major open operation far less incapacitating: "*Lumbar ureterotomy, as described in textbooks and as usually seen, is also a definitely major operation; it can and should be a relatively minor one. A method and technic for lumbar have been perfected and are described here that so minimize the operation that in this form it scarcely belongs to major surgery*" [83].

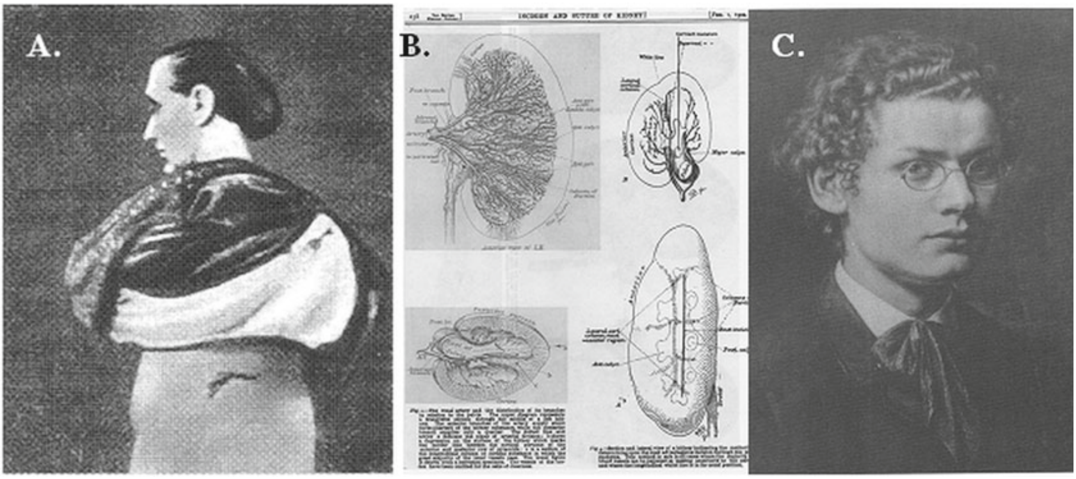

Fig. 23.3 (**a**) Margaretha Kleb (the first nephrectomy), (**b**) Brödel's white line, (**c**) Max Brödel (Max Brödel was the gifted artist and illustrator at Johns Hopkins who helped all of the "Four Doctors" and also Cushing & Young)

Staghorn Stones

Larger kidney stones were associated with infection and destruction of the kidney; once general anesthesia and aseptic surgical methods were developed, surgeons turned towards the kidney. It is no surprise that the first surgical cases on the kidney concerned stones and fistulas. Hippocrates prohibited renal surgery as being too dangerous. It was noted that in about 1680, Mr. Hobson, an English Consul in Venice, had such severe renal colic that he sought surgical advice from Domenic deMarchetti. DeMarchetti reportedly refused, but the story goes that the Consul stated, "*If you won't do the surgery, I'll keep looking until I find a surgeon who will, and I'd rather have you do it, as you're the best*" [84]. It would seem that deMarchetti studied the literature and had been performing experimental renal surgery in canines and agreed. In the records it appears deMarchetti explored through the flank but on getting to the kidney ran into too much bleeding and packed the area. He returned to surgery the second day and incised the bulging kidney: "*There was a gush of purulent matter and urine, and half a dozen stones were delivered into the wound. The patient was immediately freed of his pain, and colic occurred no more*" [84]. It was noted that there was a persistent draining fistula for years [84]. Étienne Blanchard followed this case with experimental renal surgery in dogs in 1690. The Royal Academy of Surgery in Paris had Prudent Hévin investigate nephrectomy but discovered drainage was possible but nephrectomy was too dangerous. Which leaves the legendary case of the condemned archer Bagnolete who was said to have kidney stones. The surgeons petitioned the king to allow surgery on his kidney, with the condition that if he survived, he would be set free. Supposedly the surgery actually succeeded and he was freed in 1474 [84]. Gustav Simon in Heidelberg performed a simple nephrectomy on one Margaretha Kleb for a chronic draining fistula. Simon had operated successfully on 30 dogs prior to agreeing to try nephrectomy on a human. On August 2, 1869, Mrs. Kleb received chloroform anesthesia and a lateral incision exposed her left kidney in 10 min. He ligated the entire pedicle and ureter prior to amputating the kidney. The entire procedure lasted 40 min [85]. Her postoperative course was stormy; she had a wound infection but she finally recovered: "*The picture of the obese Margaretha Kleb viewing her incision in front of a mirror is probably one of the best known medical illustrations*" [85] (Fig. 23.3a).

With kidney surgery so dangerous, results were slow, and the quickest approaches were tried initially, mostly extirpative nephrectomies. These were mostly done out of desperation, when all other modalities failed, sometimes for only a solitary but large pelvic or caliceal stone [86]. Sir Henry Morris performed the first nephrolithotomy in 1889 and Beck followed with the first pyelolithotomy. Progress was made and the stones were targeted in order to spare the kidney. Howard Kelly is regarded as one of the founding fathers of gynecology but he was a stunning surgeon. His contributions to renal stone surgery need to be mentioned. We've already quoted from his 1915 textbook. Let's turn to his discussion of renal stone surgery: "*The general rule may be safely laid down, always operate for fixed stones and for stones which cannot reasonably be expected to pass down and escape per vias naturals. Another valuable rule is always to operate when infection is present*"(vII, p. 138) [6]. He also discusses the surgical options for the surgeon upon the kidney: "*Whenever it can be done with safety, the stone in the pelvis of the kidney ought to be removed through the pelvis (pyelotomy) and not through the kidney tissue*" [6]. He notes that the pyelotomy is simpler, less bloody, and "*free from any mutilation*"(vII, p. 139) [6]. He then turns to full staghorn stones and nephrolithotomy: "*Where the stones extend out into the calices, branching in various directions, or where there is much surrounding inflammatory trouble, fixing the pelvis of the kidney, or where there is marked infection, nephrolithotomy, or the removal of the stones from the calices and pelvis through the dorsum of the kidney, is the most satisfactory operation*"(vII, p. 145) [6]. Max Brödel's figure 353 points to a plane for recommended renal parenchymal incision with illustration of the renal vasculature (Fig. 23.3b) (vII, p. 146) [6]. Kelly comments that "*The opening down onto the stone or stones is made directly inward, parallel to the long axis of the kidney, by means of blunt, flat needle armed with a single silver wire, according to the method devised by M. Broedel and worked out experimentally by E.K. Cullen and H.F. Doerge*" [87]. This has become known as the white line of Brödel. In this paper he begins, "*My studies for some years past, in operating upon numerous patients who have come to me with renal disease, have demonstrated the extreme importance of a more thorough knowledge of the anatomy of the kidney itself…*" [6]. He presents the absolute magnificent anatomical drawings that are still used today in surgical anatomy texts.

He approaches the site of incision in the kidney and continues, "*Mr. Broedel's researches have developed the important fact that the vascularization of most kidneys is provided by two arterial systems which are completely separated by the renal pelvis. There is a major system carrying three-fourths of the arterial blood providing for the anterior, and a part of the posterior half of the kidney, and a minor system carrying one-fourth of the arterial blood providing for the remaining posterior portion*" [88]. He continues and should be quoted in detail, "*Certain easily recognizable anatomical landmarks on the surface of the kidney afford a guide to this important relatively non-vascular zone sufficiently reliable for practical purpose. If the kidney is examined attentively it will always be found divided up into irregular areas (the bases of the pyramids) the size of the end of the thumb; these areas are bounded by lighter coloured lines which are often slightly depressed. These whitish lines represent the columns of Bertini, which extend up between the pyramids forming the framework which supports and carries vessels. The white lines come together in a longitudinal white line on the anterior surface, which I propose to call Broedel's white line*" [88]. Max Brödel was a young German artist originally recruited to come to Hopkins to work with Franklin P. Mall, the first professor of anatomy. Kelly found him and hired him to illustrate his prolific outpouring of surgical work (Fig. 23.3c) [89]. Incidentally, Kelly also played matchmaker, introducing Brödel to another artist, Ruth Huntington who later became Mrs. Brödel. Max was wooed by the Mayo brothers to come to Rochester in 1906, but Osler, Kelly, and Harvey Cushing urged him to stay at Hopkins to start the Department of Art as Applied to Medicine which was started in 1911. Osler was ecstatic and sent Brödel a congratulatory letter from Oxford [89].

The details of complex stone exploration and open renal surgery rapidly progressed [90].

The abilities to gain access within the renal collecting system allowed for increasing stress on the surgery to spare the renal parenchyma, because recurrence of stones was noted to be quite frequent [91]. In 1946 John E. Dees at Duke University reported on an innovative technique to aid in difficult stone surgeries [92]. He also was primarily interested in the recurrence rates following surgery and had noted that residual stones quite clearly increased the recurrence rates from to as high as 51 %. In his technique he utilized coagulum pyelolithotomy in 41 patients. All calculi were removed in 19 cases, and the remainder all had partial removal of all stones or were technical failures [92]. J. Hartwell Harrison at Harvard followed with the use of this technique in selected cases [93]. They limited the use to ten patients with multifocal small stones and was successful in all but two. One case failed because of faulty technique and one where the stone was in a walled-off calyx inaccessible to the coagulum [93].

William Boyce was born in Anson County, North Carolina, on September 22, 1918. He graduated from Davidson College and Vanderbilt Medical School prior to serving in the Italian Campaign of World War II. He was a resident at Bowman Gray School of Medicine and stayed on as faculty. He developed a lifelong interest in stone disease. By the 1960s, the team led by William H. Boyce at Bowman Gray School of Medicine began to perform complex anatrophic nephrolithotomies and intrarenal reconstructions of full staghorn stones and complex intrarenal scarring from previous surgeries [94]. The series expanded to 100 consecutive cases and they reported their long-term follow-up in 1974. Eight patients had recurrent stones with infection, seven had stones without infection, and seven had infection without stones. One patient only had a subsequent nephrectomy, and they noted that renal function either improved or remained stable in all but two of the patients [95]. Boyce would go on to study many aspects of stone disease and lead others along the pathway to stone disease, but his particular emphasis was on stone proteins and crystal-protein interactions [96]. Sadly, during the writing of this portion, Dr. Bill Boyce died on November 11, 2012, in Stuart, Virginia, at the age of 94; he truly was a legend in stone disease.

Conclusions

Urology had become the primary specialty group that was interested in urolithiasis, so the rise of urology as a specialty is important. We have already discussed many individuals who essentially restricted their work to urinary tract problems, such as some of the surgeons at the Norfolk and Norwich Hospital [97]. In addition, one of the founding fathers and Richard Bright became essentially specialists on urinary or kidney diseases. John Hunter was interested in a wide range of urinary problems but was still a general surgeon. Sir Astley Cooper certainly developed urologic interests but also was a general surgeon. Sir Henry Thompson was the one of the first surgeons to restrict his practice to urologic surgery. But it is back in Paris, France, and the Necker Hospital where the cradle of urology and specialization truly developed [98]. Jean Civiale did more than just develop lithotrity, he also parlayed his interest in genitourinary surgery to found a legacy, all based on stone disease though it would rapidly expand to all diseases of the genitourinary organs [99]. Though beginning in Paris, the specialty truly was a worldwide development with major contributions coming from a global arena inclusive to all who were interested in the urinary tract. This was true in the USA where Howard Atwood Kelley, a gynecologist, was welcomed as a founding member of the American Urological Association. We will by necessity limit this history of urology to urolithiasis.

In the second half of the nineteenth century, medical science was growing at such a rate that sub-specialization was inevitable. Leopold Dittel (1815–188) became interested in genitourinary disease at the Vienna Clinic. J.Z. Amussat in Paris began to focus on the urinary tract. Santarelli and Desault could also be mentioned and we've mentioned previously the work of Auguste Nélaton (1807–1873) who devised an improved sound and the first rubber catheter. Jean Civiale (1792–1867) in 1826 won the Acadédmie des Sciences prize for his lithotrity. The following year he received the prestigious *Prix Montyon* award. The Parisian hospital administration allocated Civiale several beds in the Necker Hospital, thereby creating the first unit for stone disease in Paris by 1824. What Civiale founded was a group dedicated to a specific disease from which emerged J. D. d'Ètiolles (1798–1860), C.L. Heurteloup (1793–1864), and Jean Casimir Félix Guyon (1831–1920). Civiale died in 1867 and the opening at the Necker needed someone to fill this void [98]. Jean Casimir Félix Guyon (1831–1920) was the first surgeon to hold a chair in urology thus making him known as the "father of urology." It is fitting he followed Civiale at the Necker Hospital [99]. A long lineage of urologic greats followed in succession. Guyon was professor and chief of urinary tract diseases from 1867 to 1906. Joaquin Maria Albarran (1860–1912) followed as professor of clinical urinary tract diseases and chief of Necker (1909–1912). Felix Legueu (1863–1939) in turn became professor of urology and chief of Necker (1912–1933). Georges Marion (1869–1960) and Roger Couvelaire (1903–1986) likewise followed the tradition [100]. Guyon left one further lasting legacy for urology; he was the guiding force for the creation of the Societe Internationale d'Urologie in 1907. It is believed that two of Guyon's protégé's Ernest Desnos and Alfred Pousson developed the idea for an international association to advance the work of specialists in urinary diseases. The first meeting took place in October 1907 to discuss and adopt rules and regulations which were written by Guyon and Albarran. It was to be an international group with four basic languages: French, English, German, and Italian. Felix Guyon was elected the first president and Watson from Boston was vice president with Harrison from London. Harrison died and Israel from Berlin took his place and Desnos became the general secretary [101].

The American urologists also came to the forefront of the new specialty. Samuel D. Gross (1805–1884) wrote the first definitive treatise on urinary diseases and surgery in 1851. William H. Van Buren became the first clinical professor of genitourinary diseases at New York University School of Medicine also in 1851. New York City literally became an epicenter for the development of urology with F.N. Otis, R.W. Taylor, P.A. Morrow, F.R. Strugis, and Edward L. Keyes, Sr. In 1888 the American Association for Genitourinary Surgeons was formed with Edward Loughborough Keyes, Sr. as president [102]. Another group of New York surgeons interested in the field of genitourinary surgery organized themselves in 1900 led by Ramon Guiteras who was professor of genitourinary surgery at the New York Post-Graduate Hospital. On February 22, 1902, the first minutes of the fledgling American Urological Association were written at Dr. Guiteras' home with founding members including the following: Ramon Guiteras, Winfield Ayers, Ferdinand C. Valentine, Terry M. Townsend, Follen Cabot, Colin L. Begg, F. W. Levasseur, and M. A. Guilber. It was open to all surgeons, obstetricians-gynecologists, and genitourinary specialists and encompassed South America and the West Indies [103]. The first meeting actually occurred in Saratoga Springs, NY, on June 13, 1902. In Guiteras' first presidential address, he defined urology from Greek, meaning urine and science [103]. In 1917 the Journal of Urology was founded as the official publication by the A.U.A. Hugh Hampton Young at the John Hopkins Hospital was the driving force and first editor: "*The title of this publication 'The Journal of Urology, experimental, medical and surgical' expresses briefly the aims, hopes and ambitions of the editors*" [104]. The Journal of Urology has been published continuously now since its first volume in 1927. There have been 188 monthly volumes, with eight editors in chief at the helm. Looking at the first 70 volumes of the Journal of Urology between 1917 and the 1950s, about 5,830 papers of which 313 were on urolithiasis or 5.4 %. A tremendous amount of clinical and research activity centered upon stone disease [105].

The Four Doctors of Johns Hopkins is a now an iconic painting that hangs in the William H. Welch Medical Library at Johns Hopkins Medical School right next to the John Singer Sargent painting of Mary Elizabeth Garrett who paid for the American painter to do both portraits.

We've discussed three of these four pillars of the early Johns Hopkins Medical School. The painting interestingly turned 100 in 2007 and has been restored three times; Sargent apparently hated Halsted and it was rumored that he painted the surgeon's face with pigments that would fade with time [106]. This has not proven to be true, but Sargent was not happy with Osler's face and repainted it again after he had finished. "*A faculty member at Johns Hopkins once remarked that there are three great institutions in the Western World: the Roman Catholic Church, the Holy Roman Empire, and the Pithotomy Club*" [107]—this statement opens a paper by William H. Jarrett II, M.D. about the now defunct medical student club that began with the very first graduating class of John Hopkins Medical School [107]. The club was for senior students with high academic honors; they met at 731 North Broadway in Baltimore and entertained the likes of H.L. Menken. They held dances and social functions that were chaperoned by Mrs. Grace Revere Osler, Mrs. Bessy Mason Colston Young, and Mrs. J.M.T. Finney, all wives of the Hopkins faculty. The handwritten constitution promotes the function of this group as follows: "*The object of this Society is the promotion of vice among the virtuous, virtue among the vicious, and good fellowship among all*" [107]. It is believed that the Pithotomy Club originated the famous "Three Fates" connotation of three of the four doctors. In a photograph by the house staff, the fates are written under each of the doctors, W. S. Atropos, Wm. Lachesis, and Howard A. Clotho. This of course caricatures these faculty members as the Greek mythologic Fates or Moirae, three goddesses who personified the inescapable destiny of man (or woman). Atropos also comes from the word Aisa, who is the cutter of the thread and literally means "she who cannot be turned," perhaps most appropriate for Halsted. Lachesis means "*apportioner of lots*" who measured the thread of life and does fit Osler. Clotho literally means "*spinner*" and she spun the thread of life which was given to Kelly [108]. One final anecdote deserves saving to the last as pointed out by Charlie Bryan, "…*in a brief notice appearing one Saturday in March 1943 in the Baltimore American, under the headline 'Liberty ship named for Dr. Osler'*" [109]. It appears that during World War II, some 2,700 Liberty ships were rapidly built and deployed as part of the US war effort. It so happens that ten such Liberty ships were named after Hopkins medical faculty: William Osler, William H. Welch, Howard A. Kelly, William S. Halsted, Franklin P. Mall, John Howland, William H. Wilmer, John J. Abel, Harvey Cushing, and William S. Thayer [109]. "*He who studies medicine without books sails an uncharted sea, but he who studies medicine without patients does not go to see at all*" [110].

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24 Epidemiology

Introduction

> "*Snares are laid for our lives in every thing we eat or drink: the very air we breathe, is loaded with contagion. We cannot even sleep, without risque of infection.*" [1]
>
> —Tobias Smollett, 1771

We have spent much of this textbook talking about stone disease in relation to the history of medicine, for truly one disease cannot fully be removed from any association with the profession of medicine in general. Here too, in our discussion of epidemiology, or the study of the patterns and incidence of disease, we cannot fully separate stone disease from medical trends. Therefore, we need to discuss infectious disease just a bit in order to elucidate the origins of epidemiology itself. For infectious diseases have shaped mankind's destiny as surly as stone disease even though both maladies are truly ancient. In prehistoric times there is some evidence that religious veneration of the river gods or naiads were asked for intercession for stone disease [2]. Herodotus wrote on the specialization present in ancient Egyptian medicine, "*The art of medicine is thus divided amongst them: each physician applies himself to one disease only and not more. All places abound in physicians; some physicians are for the eyes, others for the head, others for the teeth, others for parts about the belly and others for internal disorders*" [3]. From our discussion of Shattock's description of early Egyptian stones, we know that the bladder stone was present in a 16-year-old boy. Hippocrates might be considered the father of epidemiology, and Osler stated, "*Like everything that is good and durable in the world, modern medicine is the product of the Greek intellect*" [4]. Hippocrates and Aretaeus both noted that bladder stones were most common in young boys. Galen notes stones to be a "*malady proper to boys*." Celsus stated that he would only operate upon boys between the ages of 9 and 14, usually in the spring.

Malaria had been known for years since Roman times, with its name suggesting "*something bad from the air*." There were oriental speculations that the mosquito might be associated with malaria in Sanskrit writings of 500 CE. It appears that the Black Death started near the Aral Sea bounding Russia and China near the rooftop of the world, the Himalayas. In 1346 it was clearly noted in India spreading to Armenia, killing Tartars and Kurds. By 1347 it had reached Crimea, then Messina, Genoa, Pisa, and Venice. By Christmas of 1348 it came to Bristol, then the Highlands, and finally to London. "*How many valiant men, how many fair ladies, breakfasted with their kinsfolk and the same night supped with their ancestors in the other world?*" asked Boccaccio [5]. Hieronymus Fracastorius (1483–1553) had discussed in his treatise *De Contagione* that disease and epidemics were sown like seeds. He suggested that these should be called "*fomites*" and could be transmitted in the air, water,

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clothing, food, or combs [6]. On September 17, 1683, Antonie van Leeuwenhoek from Delft looked at a drop of fluid that he removed from his own teeth and noted bacteria in clumps and chains and immediately began to write to his colleagues at the Royal Society. He quickly added some mathematical calculations suggesting that these little animalcules were "*more numberous than the population of the Netherlands, all moving about delightfully*" [7].

The Industrial Revolution brought about changes in the quality of life and raised people to different social classes, which in turn led 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 with 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. But by Alexander Randall's time, people were again returning on the thought that stone disease was perhaps a manifestation of an infectious etiology. There were many investigators in the early twentieth century that assiduously looked for an infectious etiology. How ironic would all of this history become if stones were in fact the formation product of a primitive bacterium, such as the hypothesized nanobacteria. The NASA rover "Curiosity" has recently discovered something significant in the huge Gale crater, but this so far is nothing compared to McKay's announcement of a possible life-form from the Martian meteorite ALH84001 on August 16, 1996 [8].

Rise of Epidemiology

> "*Latona's son a dire contagion spread,*
> *And heap'd the camp with mountain's of the dead.*" [9]
>
> Homer, Iliad, Book I

Thomas Sydenham (1624–1689) deserves our attention again briefly at the outset because he so clearly linked stone disease with familial tendencies and development of the gout. Sydenham probably left academics and Oxford because of the influence of Robert Boyle [10]. His interest in medicine allowed him to use his own powers of observation to develop his unique notions about disease. He published his observations in his 1676 book *ObservationesMedicae* [11]. He wrote of suffering from the gout, "*The victim goes to bed and sleeps in good health. About two'clock in the morning he is awakened by a severe pain in the great toe; more rarely in the heel, ankle, or instep. This pain is like that of a dislocation…Then it is a violent stretching and tearing of the ligaments—now it is a gnawing pain and now a pressure and tightening…He cannot bear the weight of bed clothes nor the jar of a person walking in the room. The night is passed in torture, sleeplessness, turning of the part affected, and perpetual change of posture; the tossing about of the body being as incessant as the pain of the tortured joint*" [12]. He proceeds to discuss stone disease, "…*the gout breeds the stone in the kidney of many subjects either (1) because the patient is obliged to lie long on his back, or (2) because the secretory organs have ceased performing their proper functions; else (3) because the stone is formed from a part of the same morbific matter*" [12]. He continues to speculate that alcohol and rich foods might have a specific causative action on producing stones. Sydenham's careful observations on the relationship of stone disease to gout are some of the earliest in the epidemiology of urolithiasis.

George Baker (1722–1809) was educated at King's College, Cambridge, and began to practice medicine in London around 1761. He was successful becoming a member and eventually president of the Royal College of Physicians. He presented some fascinating work that he performed investigating a devastating condition "*Devonshire colic*" that was caused by lead poisoning from the cider manufacturing process. His investigation resulted in the removal of lead and resolution of this problem. He became the physician of King George III, attending him during his bouts of madness, and was created the Baronet Baker of Loventor in Totnes, Devon, on August 26, 1776 (George III voided blue urine, but more on this in Rarest Stone chapter) [13]. We finally come to the last of the big four of Johns Hopkins with William H. Welch who introduced Sir John Simon's comments on George Baker with the following comments: "*The disease which was in question, the associated colic and palsy of Devonshire, was one of serious danger to those who suffered it; and it was so frequent in the county that, for instance, the Exeter Hospital alone during the years1762-7had among its in-patients an annual average of nearly sixty cases of it*" [14].

Demography

John Graunt (1620–1674) was born in London on April 24, 1620, to Henry Graunt who was a storekeeper in Hampshire and his wife Mary (Fig. 24.1a). John was the eldest of seven or eight children, and he apprenticed with his father as a draper (like van Leeuwenhoek). He married Mary Scott in February of 1641 and he became quite prosperous soon becoming involved in politics. It is probable that during his interlude with serving his community that John Graunt first became seriously interested in statistics and mortality. He conceived the notion to write a treatise on mortality statistics and wrote *Natural and Political Observations mentioned in a following index, and made upon the Bills of Mortality With reference to the Government, Religion, Trade, Growth, Ayre, diseases, and the several Changes of the said City* (Fig. 24.1b) [15]. The Bills of Mortality for London were first compiled by order of Thomas Cromwell about 1538, and the keeping of them was commenced by the Company of Parish Clerks in the great plague year of 1593. The bills were issued weekly from 1603. The charter of the Parish Clerks Company (1611) directs that "*each parish clerk shall bring to the Clerks' Hall weekly a note of all christenings and burials*." Charles I in 1636 granted permission to the Parish Clerks to have a printing press and employ a printer in their hall for the purpose of printing their weekly bills. Graunt noted that the London statistics actually began in 1592 and fell into disuse but were taken up again by 1603. Graunt spent a great deal of time studying the statistics compiled in the Bills of Mortality, and on February 5, 1662, he published his 90-page summary of the facts with his commentary. This was distributed to members in attendance at a meeting of the Royal Society. Graunt described his own work as "*to have reduced several great confused volumes into a few Tables, and abridged such Observations as naturally flowed from them, into a few succinct*

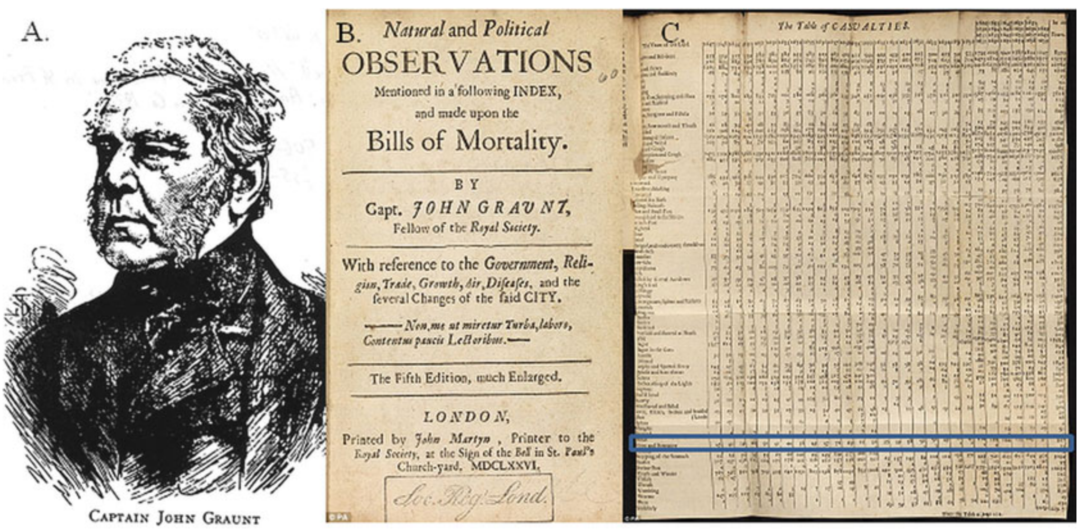


Fig. 24.1 (**a**) Image of John Graunt, (**b**) his frontispiece from his 1662 textbook, C. Graunt's tabulations of mortality showing death from stone disease

Paragraphs, without any long series of Deductions" [15]. Graunt is considered as the first person to have utilized demographical statistics to study human populations. He was made a charter member of the Royal Society and his work was widely discussed. His life table might also be considered the beginnings of life insurance and the prodromus for actuarial science.

Graunt has become a rather iconic figure in the development of epidemiology and in the opinion of Professor Kenneth J. Rothman "*he added more to human knowledge that most of us can reasonably aspire to in a full career*" [16]. Looking specifically at stone disease, Graunt addressed the risk of death by stone disease in his monograph. Taken from his first edition from 1662, Fig. 24.1c depicts the diseases and casualties from the year 1632. There are two sections that call our attention to stone disease; one is "*cholick, stone, and strangury…56*" and the second "*cut of the Stone…5*" [15]. Of course the first group could include biliary disease and urinary retention not secondary for stone disease, but Graunt had a category for jaundice that probably eliminated the biliary causes. In any event, stone disease and related surgical deaths ranked 17th on the total causes of death in London in 1632. The number one cause of death was in infancy, fourth was old age, and seventh was stillborn or abortive deaths. Almost all of the others are infectious in nature. Death from stone disease trumped deaths by accidents (56 vs. 46). Graunt in his book also mentions briefly the stone on page 29 of this work: "*Now the Stone, and Strangury, are diseases, which most men know, that feel them, unless it be in some few cases, where (as I have heard Physicians say) a Stone is held up by the Filmes of the Bladder, and so kept from grating, or offending it*" [15].

A near contemporary to Graunt was the physician Bernardino Ramazzini (1633–1714). Ramazzini was born in Carpi, Italy, in 1633 and became a medical student at Parma University. He wrote his magnum opus in 1700 *De Morbis Artificum Diatriba* from Modina [17]. He was appointed the chair of the theory of medicine at Padua in that same year where he taught for the rest of his life, where he died on November 5, 1714. He is the one of the first physicians to present evidence against smoking and tobacco in his chapter on "*Diseases of Tobacco-workers*." He discussed silicosis but decried his inability to effectively investigate this trade because of local superstitions: "*I wished to have opened the cadaver of some chalk worker but neither a request nor money can induce the people of Modena to permit the opening of the bodies of those who died from an extraordinary disease*" [18]. Bernardino was the first to describe the stress and "burnout among professionals" including physicians and surgeons [19]. Sadly, Ramazzini noted no predilection of stone disease amongst astronauts, teachers, nurses, and others whom are now known to have such risk factors from not drinking enough fluids, but he is considered the father of occupational medicine [20]. But Ramazzini did observe that Aristotle misstated that only man suffers from renal and vesical calculi; he had observed these in animals as well. He also mentioned that "*Butchers have very often observed that stones may be found in the stomach and the guts of oxen [*bezoar stones*], and this observation contradicts Aristotle's opinion that no animal but man suffers from stones, unless one thinks that Aristotle spoke only about stones in the kidney*" [17].

In the eighteenth century, global exploration progressed rapidly as nautical capability became increasingly sophisticated. The problems of long voyages had been hampered by the deaths of thousands of seamen on these expeditions secondary to scurvy. James Lind (1716–1794) while on board the *HMS Salisbury* performed the critical experiment on scurvy by dividing twelve men into groups of six pairs. Each group received cider, seawater, elixir of vitriol, vinegar, a purgative mixture, and oranges and lemons for 14 days [21]. There was a dramatic recovery of the men on the oranges and lemons though some improvement was noted on the cider. His famous paper in 1753 noted these results; however he did not fully recognize the implications from his own findings [22]. Percivall Pott (1714–1788) noted the predilection of tumorous ulceration of the scrotum of chimney sweeps in 1775 [23]. Edward Jenner presented his careful work on inoculation with cowpox against the fatal disease smallpox in 1798. He first tested his hypothesis on an 8-year-old boy, James Phillips, on May 14, 1796 [24]. It took more than 80 years after Jenner's pioneering work to develop newer vaccines, and a vociferous anti-vaccination movement emerged along with colorful cartoons of vaccinated infants growing cutaneous cows, but by 1977, led by Donald Hender, the World Health Organization finally declared the eradication of smallpox after the last naturally occurring case was reported in Somalia [25].

Thomas Beddoes (1760–1808) was an English physician perhaps more famous because he taught chemistry to Sir Humphrey Davey who later would become famous in the Royal Institute. He founded the Pneumatic Institution for the study of gases and their chemistry. He also began to question the dogma that had stymied medicine's progress. In a famous letter to Sir Joseph Banks, the head of the Royal Society, "*On the Causes and Removal of the Prevailing Discontents, Imperfections, and Abuses, in Medicine*" in 1808, Beddoes argued that there was an urgent need to systematize, collect, and index all medical facts so as to better evaluate their merit [26]. "*Why should not reports be transmitted at fixed periods from all the hospitals and medical charities in the kingdom to a central board?*" [26] He believed that the data could be made freely available to physicians and could be further open for study and experimentation: "*To lose a single fact may be to lose many lives. Yet ten thousand, perhaps, are lost for one that is preserved; and all for want of a system among our theatres of disease, combined with the establishment of a national bank of medical wealth, where each individual practitioner may deposit his grains of knowledge, and draw out, in return, the stock, accumulated by all his brethren*" [26]. Beddoes, like many other enlightened physicians, was painfully aware the effective armamentarium of the physician could do little to actually help his patients. He was literally calling for a system of scientific investigation of disease and therapeutic treatment that could alter the way medicine was practiced. He was a physician again ahead of his time, but times were changing quickly.

The French School and Medical Statistics

> "*I am glad I know what great men are. I am glad I know of what they are made, and how they made themselves great, though this knowledge has broken the last of my household gods; yet it has taken away the flaming swords that stood before the gates of this Paradise, where may still be seen the track of the serpent and of the devil himself, so I will keep out of bad company.*" [27]
>
> Dr. John Y. Bassett, Huntsville, AL (Osler's Alabama student)

Following the French Revolution, medicine no longer rested on the hierarchical laurels of past giants, and the French physicians began to systematically attack the centuries of dogma and rise to forefront of medicine. Osler commented, "*Writing in the American Medical Recorder, July, 1821, an American student, Dr. F. J. Didier, said of the Paris professors of that date, 'They were always talking of Hippocrates, Galen, Celsus, & c., as if not a particle had been added to the stock of knowledge since their time.' And again, 'The doctrines of John Brown, mixed up with the remnants of humoral pathology, form the basis of the present system*" [27]. This was all about to change. Bichat became the person insisting on observation and investigation followed by Broussais, Andral, Chomel, Velpeau, and Helmagrande who completed the rise of French medicine and the reawakening of the inquiring mind. They attracted dedicated young medical professionals from around the world to their teaching hospitals, La Charité and La Pitié.

Pierre Charles Alexandre Louis (1787–1872) came to Paris to practice medicine, investigate disease, and teach. He was born on April 14, 1787, in the small town of Ay in France. He studied medicine outside of the Paris elite physicians and first practiced for several years in Odessa. He became frustrated by his inability to treat patients effectively and decided to come to Paris where he would dedicate himself to studying diseases. He was now aged 32 on his return, "*He entered the hospital of La Charité as a clinical clerk, under his friend, Professor Chomel. For nearly seven years, including the flower of his bodily and* *mental powers (from the age of thirty-three to forty), he consecrated the whole of his time and talents to rigorous impartial observation. All private practice was relinquished, and he allowed no considerations of personal emolument to interfere with the resolution he had formed…No sooner, however, were his facts sufficiently numerous to admit of numerical analysis than all doubt and hesitation were dissipated, and the conviction that the path he was pursuing could alone conduct him to the discovery of truth became the animating motive for future perseverance*" [28]. The result of his concentrated efforts during this time was in 1823 treatises on small intestinal perforation, croup in adults, and communications between the right and left sides of the heart. In 1824 he published on the pathology of mucous membranes of the stomach and pericarditis. In 1825 he wrote up his *Anatomical Researches, & c, on Phthisis* which became a landmark work on tuberculosis. In 1826 he continued his brilliant outpouring of work with a study on abscess of the liver, on the bone marrow changes in Pott's disease, a paper on sudden and unforeseen deaths, one on chronic, slow anticipated deaths, and a paper on treatment of taenia [29]. His monumental work of 1829 was the *Anatomical Pathological and Therapeutical Researches upon the disease known under the name of gastro-enterite, putrid, adynamic, ataxic, typhoid fever, & c., compared with the most common acute disorders* [30]. This work was based upon the autopsies and detailed clinical observations of 138 patients made from 1822 till 1827. This work was translated into English by one of his American students, H.I. Bowditch in 1836.

Louis moved on with his new *Numerical Method* of looking at disease to one of the most common treatments utilized by physicians for centuries, bleeding. One of Louis's senior contemporaries was Joseph Victor Broussais (1772–1838) who believed that all fevers arose from a common cause, a manifestation of inflammation to the organs. Hence, the treatment of most illnesses consisted of bloodletting. In fact, following the French Revolution, bloodletting for treatment had risen to unprecedented heights. Patients were bled liberally and leeches were applied for almost all illnesses. One of Louis's own students, J. J. Jackson, noted, "*If anything may be regarded as settled in the treatment of diseases, it is that bloodletting is useful in the class of diseases called inflammatory; and especially in inflammations of the thoracic viscera*" [31]. Bloodletting could occur by a variety of methods such as venisection, arteriotomy, cupping, and by application of leeches [31]. In just the year 1833 alone France imported 42 million leeches, and it has been estimated that these alone accounted for five million liters of blood being removed annually. Recall that 67-year-old George Washington in retirement was bled copiously (estimates are up to 3.75 L or 80 oz) in just 12 h when he developed epiglottitis in 1838 [32]. This is significant because it puts into perspective William Cheselden's comments regarding the bleeding of a stone patient which will be quoted in detail as follows:

> "*A remarkable case of a person cut for stone in the new way, commonly called the lateral; by William Cheselden Esq, surgeon to her late Majesty; communicated to Martin Folkes Esq F.R.S. by Mr. Reid, surgeon at Chelsea who attended the cure. Mr. Simpson, of Little Ormond Street aged seventy five, after having been afflicted with the stone above five years, and taking Mrs. Steven's medicines about a year before for seven months successively without receiving any benefit, was cut by Mr. Cheselden March 13,1741-2 at which time he had a fit of stone upon him which had continued for ten days.- At his own earnest request after consultation the operation was performed, and a large flattish stone was extracted, weighing very near four ounces. The wound bleeding plentifully from small vessels, only a piece of thin wet sponge was introduced, that it might bleed for a while through; intending if there should be occasion to tie any vessel afterward that should require it. But contrary to expectation this proved the means of stopping the effusion of blood; and from experience in many cases since it has been observed that nothing is so useful as this method (this accidentally discovered). About six hours after the operation, the patient having lost but little blood, it was thought proper to take twelve ounces of blood from his arm.- In five weeks he was perfectly cured and continues to this day without any return of his distemper*." [33]

Bleeding had assumed the primary method of treating patient at this time, and Louis did not really question bleeding; he simply was curious to investigate whether the timing of bleeding had any significant effect on the longevity and outcome of the illness. What Louis really doubted was the validity of Broussais's theory and he set about a controlled study of bleeding. His first publication of this was *Research on the effects of bloodletting in some inflammatory diseases* in 1828 [34]. The paper was revised and amplified, and he published a text which appeared in 1835 with an English edition in the following year [35]. Essentially, Louis chose 77 patients for bloodletting who all had well-characterized pneumonia. He next established the onset of their disease, the frequency of their deaths, and the timing of bloodletting (early first 4 days vs. late—after 4 days). This division resulted in 41 patients treated early and 36 patients treated late with comparable ages in both groups. He discovered that patients that were bled early recovered faster (average of 3 days shorter illness), but a surprising "*three sevenths*" (44 %) of the patient bled early died compared to "*only one fourth*" (25 %) of those bled late. This resulted in his famous comment that this was "*startling and apparently absurd*." He would go on to make several conclusions, but of interest to us here the main point was as follows: "*I will add that bloodletting, notwithstanding its influence is limited, should not be neglected in inflammations which are severe and are seated in an important organ; both on account of its influence on the state of the diseased organ; and because in shortening the duration of the disease, it diminishes the chance of secondary lesions*." Old knowledge dies hard; he had a hard time himself believing his own data. Bleeding was slowly declining and even the stone sufferer did not have much longer to deal with this worthless and even hazardous treatment for much longer. Jules Gavarret followed closely in the wake of Louis and began the formal introduction of statistics using the principles of Pierre-Simon Laplace (1749–1827) and Siméon-Denis Poisson (1781–1840), calling them *le calcul des probabilités* [36].

Pierre Louis's major contribution to the advancement of medicine might well be the students he attracted to study with him in Paris, and they came from everywhere (Table 24.1): "*Louis possessed a singular power of attracting hard-working, capable men, and this in spite of the fact that his rivals and friends, Chomel and Andral, possessed more brilliant gifts of a certain kind*" [28]. In the aftermath of the rise of elite Parisian physician, teachers would develop a renaissance in stone disease treatment. Fourcroy would begin a serious investigation into the chemistry of stone disease, begin to explore the prevalence in humans and in animals, and start a stone registry from widespread and diverse institutions in order to gather data. All of the pieces of the puzzle were now in place awaiting the coming of Jean Civiale.

Table 24.1 Pierre Charles Alexandre Louis's legacy by individuals whom he trained

William Farr, William Guy, and William Budd (all students of Louis) founded the Statistical Society of London in 1834
Americans included: Boston: James Jackson, Jr., H.I. Bowditch, Oliver Wendell Holmes, Sr., George C. Shattuck, Jr., John D. Fisher, J.C. Warren, J. Manson Warren. New York: John A. Swett, Abraham Dubois (father of pediatrics), Alonzo Clark, Charles L. Mitchell, Charles D. Smith, Valentine Mott, Sr., John T. Metcalfe. Philadelphia: George W. Norris, W. W. Gerhard, Caspar W. Pennock, Thomas Stewardson, Alfred Stillé, Thomas D. Mütter (famous museum), E. Campbell Stewart, Charles Bell Gibson, John B. Biddle, David H. Tucker, Meredith Clymer, William P. Johnston, W.S.W. Ruschenberger, Edward Peace, William Pepper (primus). Baltimore: William Power. South: Peter C. Gaillard, Gibbes, Peyre Porcher, J.L. Cabell, L.S. Joynes, Selden, Rudolph, John Y. Bassett (Alabama Student) (Osler on Louis: Alabama Student)
Oliver Wendell Holmes and George Shattuck, Jr. (with Shattuck's student, Edward Jarvis) founded the American Statistical Society in 1851

Stone Disease: The Earliest Trends

We have already met Matthew Dobson (1732–1784) in past chapters, but it is time to consider his monumental contributions to the epidemiology of urolithiasis. Dobson was born in Yorkshire, the son of a nonconformist minister, and was expected to follow in his father's footsteps. He however discovered medicine as a career in Edinburgh where he graduated in 1756 [37]. He came to his clinical practice in Liverpool in 1762 and became one of the founding physicians at the Liverpool Infirmary in 1770. He was interested in urinary stone disease and corresponded widely with the Royal Society and published in the Philosophical Transactions. 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 30 times higher than those admitted to Cambridge Hospital. In Worcester, Hereford, and Exeter hospitals, there was 1 stone patient among 394 admissions. In North East England including Newcastle, York, Leeds, and Manchester, the ratio was 1/420. In Liverpool, Chester, Shrewsbury, and North Wales, it was 1/3,223. He concluded that stone disease was more common in the "*Cyder*" districts and that hard water prevents rather than promotes the formation of stone disease. This information is counterintuitive and flies against practical belief. He wrote his treatise "*A Medical Commentary on Fixed Air*" in 1779, Chapter 9 is called "*On the disposition of the stone in the cyder counties, compared with some other parts of England*" [38].

We have also met with another surgeon, Alex Copland Hutchison, who wrote a treatise on stone disease on May 4, 1830, entitled, "*A Further Inquiry into the Comparative Infrequency of Calculous Diseases Among Sea-Faring People, with some observations on their frequency in Scotland*" [39]. This work broadly expanded the limited statistics of Dobson and pursued a hypothesis that seafaring people rarely formed urolithiasis. Hutchison in fact also utilized the data from the national census that was first carried out in the United Kingdom in 1801. In this published review, Mr. Hutchison discussed the trend for decreased incidence of stone formation in sailors in the British Navy. In addition, he extended his data by surveying some of his fellow surgeons all around England and Ireland to tabulate the basic numbers of stone patients in port cities. He compared the incidence in Dublin, another port city, to the incidence of stone disease amongst Roman Catholic priests, thus using the clergy as the control to clearly show that stones were more common in the terrestrial clerics. He also quoted a study by Dr. Egan from the Transactions of the Royal Irish Academy on the incidence of stones in Roman Catholic priests. Hutchison noted, "*I feel assured, indeed, with my lamented friend, Dr. Marcet (recently died), that it is chiefly in this way that the true pathology of the disease can ever be obtained, and, consequently, the most efficacious mode of treatment*."(120) [39].

John Green Crosse is another surgeon from Norwich who doubted the findings of Hutchison as did most investigators of the time. We've referenced Crosse on numerous previous occasions but his 1835 work "*A Treatise on the Formation, Constituents, and Extraction of the Urinary Calculus*" [40]. Crosse suggested that stones affect males significantly more than females, and that there was an age distribution for the formation of stones that starts at a young age (Yelloly will quantify this for us later). Finally, we should note that an American author and investigator, Samuel D. Gross's "*Practical Treatise on the Diseases, Injuries, and Malformations of the Urinary Bladder, the Prostate Gland, and the Urethra*" in 1851 discussed epidemiology of urolithiasis [41]. Gross displayed significant interest into the regional distribution of stones in 8,574 patients from England, India, the United States, Moscow, and France (166). He utilized some unique sources for data from such isolated regions as from Egypt (Professor Reyer) as well as from Dr. Livingstone on Central Africa (168) [41].

Stone Disease and the Norwich School

The earliest epicenter spot for the epidemiology of urolithiasis is the Norfolk and Norwich Hospital that we've already discussed in the previous chapter on Stone Hospitals. Recall that it was founded by the aid of an early lithotomist, Benjamin Gooch. A six-man committee in August 1770 convened and laid plans for the hospital in an open meeting at Guildhall, Norwich [42]. The hospital originally had 100 beds and was a "state-of-the art" institution. The number of beds was increased to 200 beds when the hospital was rebuilt in 1879–1883.17 All patients admitted were recorded, and the hospital kept a special register for stone cases. The original register has not survived but the Reverend C. J. Chapman presented to the hospital a vellum-bound book containing a copy of the original entries in 1819. This historical legacy is called "*A Record of the Stones Patients in the Norfolk and Norwich Hospital. Not to be Taken Away*." A second register of the stone patients was begun called "*Norfolk and Norwich Hospital Catalogue of Calculi 1909*" which documented the stone series until the very year that the stone epidemic subsided [43]. On February 20, 1773, the hospital had been opened for a mere 7 months when the governors voted to provide the "*Apothecary do provide a suitable nest of drawers to deposit the stones extracted in this House, in order to show to strangers, and to be referred to occasionally- and none suffered to be taken away*" [43]. This information is somewhat redundant, but it becomes the foundations of the first epidemiologic studies of urinary calculi that have been gathered.

We also know that Alexander Marcet later endeavored to develop a central repository for stone disease information including pathologic specimens that could be analyzed and information about the patients' history and their diets which could be correlated to the stone analysis similar to what was occurring in Norwich. Marcet opened his comments by stating, "*Physicians and chemists from Galen to Paracelsus to Van Helmont and Boerhaave were unable to form any rational conjectures on the composition of urinary calculi*" [44]. He even proposed to start an international consortium using Berzelius as the lead investigator. In his text he described a detailed clinical history from patients that would serve as the prototype for gathering useful information about the patient's themselves. In another chapter he described his statistics from Norwich Hospital from1772 to 1816 (44 consecutive years) and used this institution as his model for English centers. He extensively reviewed all of the relevant prior published investigations (including the French—difficult to get because of the war years) and agreed with Dobson's observations that hard water appeared to reduce the risk of stone formation. He estimated the surgical interventions at various London institutions over 10 years as follows: St. Thomas's 1/528 patients, St. Bartholomew's 1/340, and Guy's at 1/300. He compared this data to the Parisian Hôpital de la Charité at 1/250, giving our first international surgical rates [44]. Marcet concluded regarding the Norwich Hospital in 1817, "*In my enquiries I have met with great disappointments…it will appear scarcely credible that in the larger hospitals in London, St. Bartholomew's, St. Thomas's, Guy's and the London Hospital, no regular or at least no ostensible records of the cases of lithotomy which occur in them should be preserved. It is with great pleasure, however, that I am enabled to mention one striking exception to this unaccountable oversight in public hospitals. The Norfolk and Norwich Infirmary in this and several other respects, stands as a model of regularity and good management*" [44]. Jean Civiale in Paris described "*labelle et riche collection de Norwich*" in 1863. Sir Henry Thompson wrote also in 1863 called Norwich "*the most perfect and complete record, literally graven in stone, that the world possesses of calculous experience*."

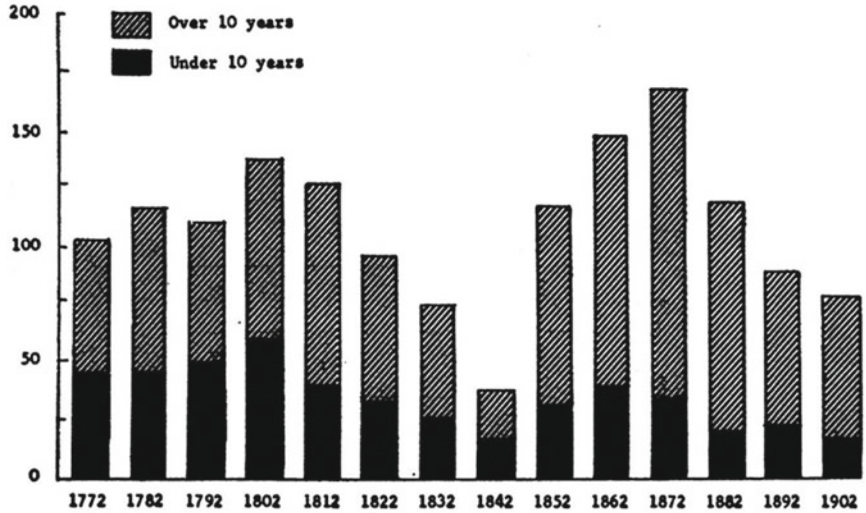
John Yelloly yet another Norfolk and Norwich physician nearly completed this historical inquiry into the epidemiology of urolithiasis. We have already noted that he performed more detailed studies on the famous Norwich School's stone collection and presented in two papers to the Royal Society in 1829 and 1830. Yelloly's first paper on the Norwich stones is entitled *Remarks on the Tendency to Calculous Diseases; with Observations on the Nature of Urinary Concretions, and an Analysis of a Large Part of the Collection Belonging to the Norfolk and Norwich Hospital* [45]. In part one of this paper, Yelloly concentrated on the incidence of this disease among the county of Norfolk. He presented his statistics for the hospital noting that it had been opened for a mere 56 years and 649 lithotomies had been performed, "*more than 11½ per annum*" [45]. Stone disease represented 1/40 hospital admissions and he calculated the incidence in the county to be 1/34,000 inhabitants (575 patients out of 351,000). He calculates that those living in the city of Norwich are even more at risk of stone disease 1/21,000, and he proceeds to look at individual areas such as Lynn, Yarmouth, Taverham, Tunstead, and Walsham. He looked at the change in the population during this time and noted that the proportion of calculous cases had actually diminished as the population increased. He quoted the works of others who had also looked at the Norwich numbers of Dobson, Marcet, and Smith. He now began the assault upon Copland Hutchison's assertion that the "*sea-faring life being remarkable for the comparative infrequency or urinary calculi*" [45]. Yelloly then looked at ages of life and notes a trend for more children having stones in the metropolitan city than those rurally in the country. He never speculated upon this observation that would eventually lead to the root cause of endemic bladder stones. He also presented the mortality data from lithotomy. Surgery was risky, 1 in 7.29 cases died, even in a center with highly skilled surgeons. In the most recent years, with the adoption of the lateral lithotomy of Cheselden, the rate was reduced to 1 in 8.42 "*which differs very little from the average of CHESELDEN, whose improved lateral operation they followed*" [45]. He also noted the mortality increased with the patient's age. He calculated tables of mortality that were both age and gender specific. In 292 cases the patient was under the age of 14, in 155 the age was from 14 to 40, and in 202 cases the patient was over 40 [45].

The second part of his 1829 paper was titled Part II.—Of Urinary Concretions [46]. In this section he presented his detailed chemical analysis of 330 of the 649 specimen stones from the collection. In his own words he stated, "*Within the last four or five years, a certain portion of the calculi have been divided; and these, as well as such as were broken in the extraction, amounting together to about 330, I have carefully examined*" [46]. He used the classification of Wollaston and Marcet in reporting each type, layer by layer. Lithic acid (uric acid) was noted principally in 81, lithate of ammonia in 20, oxalate of lime in 20, phosphate of lime in 4, and fusible (mixed struvite and carbonate apatite) in 37 of the patients with a predominate single stone type ($n = 162$ stones) [46]. He noted, "*…that about one half of the specimens are composed of one description of material only; and that the remainder consist of alternating layers, more or less numerous of most of the substances of which human urinary calculi are composed*" [46]. He spent the final portion of this part discussing the chemistry of each of the species of minerals common to urinary calculi. He believed that lithic acid is the most significant element in human stone disease but speculated that the oxalate stones might be important, especially in animals, and noted that rats and pigs had these types of stones. Finally, A. Batty Shaw would tabulate all of the Norfolk and Norwich Hospital and make the deduction about the end of endemic stones in the region (Fig. 24.2a). He also documented the rise and fall of the various surgical operations for bladder stone (Fig. 24.2b). In these figures Shaw notes two significant observations that we will quote in full here, "*The presence of an additional aetiological factor in the older cases is indicated by the bi-modal form which the columns in Figure 2 display with a peak in the 60–70 age group. This second peak reflects the role which prostatic gland enlargement played in the aetiology of the Norwich series of stones. Bladder stones at the present time are mainly encountered in the presence of bladder outflow obstruction, most commonly due to prostatic gland enlargement; it therefore tends to be argued that prostatic gland enlargement was the sole explanation for stones among the older age groups in the past. But the presence of an additional factor, possibly the same factor that produced the high incidence of stone among the young age groups, is strongly suggested by Figure 4 which shows not only the disappearance of bladder stone in children in Norfolk at the beginning of the twentieth century but also a fall in the number of stone cases among patients of all ages*" [43].

Civiale's Data

> "*Non numerandae sed perpendendae observationes.*"
>
> —Morgagni

Fourcroy had already stimulated interest in stone disease and had at the Societe Royale de Medecine in 1786 an open competition to compare stones a



b

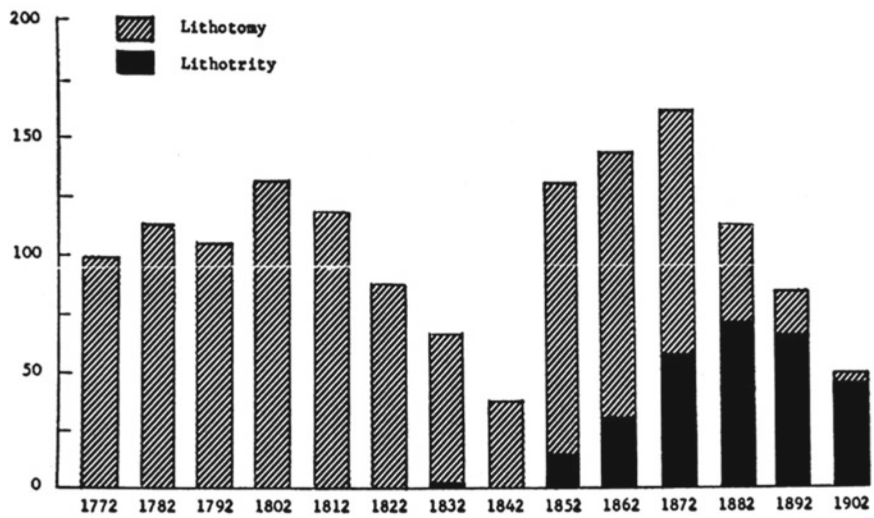


Fig. 24.2 The Norfolk and Norwich Hospital's trends on patients presenting for surgery between 1772 and 1909 representing 1,488 cases of bladder stones. (**a**) Fall in numbers, (**b**) the distribution of lithotomy versus lithotrity [43]

and bones mineralogically [47]. In 1801 Fourcroy published an 11-volume set on chemistry with 67 pages dedicated and summarizing the current knowledge of stone disease. Fourcroy also wrote a treatise that stated that bladder and kidney stones were essentially similar. He organized his clinical colleagues around France to send him stones plus relevant data on the environment, geological information, and urine information. He eventually collected over 600 stones for his continued studies [48]. In 1802, Fourcroy published his extensive research on stone disease. He identified 12 constituents in stones (7 of these in human stones) [49]. These 12 species were as follows: uric acid, ammonia urate, calcium phosphate, magnesium ammonium phosphate, calcium oxalate, and animal matter (gelatin) or combinations of these. He believed that uric acid was the most common substance in stones. He classified these seven human constituents into

Table 24.2 Comparative incidences of forms of urinary lithiasis

Form of lithiasis	Incidence in the United States
Pure calcium oxalate stones	33 %
Mixed calcium oxalate and phosphate	34 %
Pure calcium phosphate	6 %
Magnesium ammonium phosphate (struvite) these are virtually all mixed	15 %
Uric acid	8 %
Cystine	3 %
Artifacts and other	1 %

three categories. One was uric acid and its sodium and ammonium salts. Second were mineral salts. Here he noted calcium phosphate, magnesium ammonium phosphate, and calcium oxalate. He stated that calcium oxalate was often the main component of kidney stones, and he also noted small crystals of this in human urine. He hypothesized that calcium oxalate might be the nucleus that begins accretion of all stones. His incidence of stone types was as follows: 25 % were predominately uric acid, 25 % were calcium oxalate, and the rest were mixtures [48]. These numbers are eerily similar to modern series (Table 24.2). He concluded his paper by speculating that oxalic acid was normally made somewhere in the lining of the urinary tract, in this was wrong.

Jean Civiale's (1792–1867) reputation as a surgical innovator and leading light of French specialization certainly did not hurt his ability to collect and investigate the data that had been gathered since Fourcroy's time. He had already performed his first lithotrity on a living patient on January 13, 1824, with a crowd of spectators watching; he was flawless. As mentioned previously in the section on the Norwich School of Lithotomy, Civiale was keenly aware of the records kept at this institution and tried to replicate this information throughout Europe. He was aware of the study by Matthew Dobson (1799), Alexander Marcet's work of 1817, and John Yelloly's from 1828 to 1829. He utilized the sponsorship from the Ministry of Public Instruction to gather information on stone disease and lithotomy. In 1835 he produced the first European large scale statistical data which he immediately utilized to compare his new technique to the standard lateral perineal lithotomy. He had performed his new lithotripsy procedure on 43 patients between 1823 and 1827 which he claimed a complete success rate in 42/43. He now wished to compare his numbers to those he had collected from around Europe.

In this presentation to the Académie des Sciences, he compares his series of 257 patients to 5,715 lithotomies. His expanded data showed that 6/257 patients with lithotripsy died (2.3 %) vs. 1,141 or 20 % for lithotomy. Civiale also noted that there were 100 cases following lithotomy where the patients had long-term sequelae "*infirmities beyond repair as a result of the operation*." The French National Science Academy urged by factions immediately responded with their own statistical inquiries also published in that year [50]. It is interesting to note that the reporter, Francois-Joseph Double (1777–1842), was a well-known physician and one opposed to the new mathematical methods arising in medicine. Dominique-Jean Larrey (1766–1842) was a physician-chemist also interested in stone disease. These physicians and mathematicians were skeptical about the applied mathematics to medicine, though synchronous to these studies Pierre Charles Alexandre Louis (1787–1872) was pioneering statistics in studies on phthisis (1825) and typhoid fever (1828) and coined the term *method numérique* that profoundly changed all of medicine [51]. In 1828 Civiale studied the records for the incidence of bladder stone from 20 countries, mainly from Europe, based upon the known hospital cases and related this to population figures. His final argument in favor of his new method of lithotripsy was "*And to complete the demonstration of the superiority of lithotripsy over lithotomy, it can be added that since the discovery of lithotripsy, among a fairly large number of physicians suffering from calculi, hardly any can be cited as having resorted to lithotomy: all were operated on by lithotripsy*."

The panel began their response as follows: "*Calculi of the bladder are for the human race, and some more so for male individuals, one of the most intolerable diseases that life can be* *afflicted with. In addition to the pain and the dangers of the condition, and the pain and dangers of treatment, there are also certain moral feelings, predisposing the soul to sadness, which are closely bound to the affliction, and constitute a complication of varying seriousness to this so distressful state*" [50]. This could well be Larrey who was interested in stone disease. They continued with quite detailed and specific problems with M. Civiale's data. It is also mathematically quite sophisticated (probably the influence of Poisson). First and foremost much of his data was derived from the numbers of Raw [Rau] of Amsterdam 1,547 cases, Brother Jacques 4,500 cases, Baseillac 316 cases, Le Cat 310 cases, and Pouteau 150 cases. They also noted that he excluded the data from Marcet, Smith, Prout, and Yelloly in his calculations. They specifically note that those used by Civiale are less well documented than those that he chose to exclude [50]. They are hinting perhaps of a biased approach to his data selection. They broach the topic of statistics in medicine as follows: "*Medicine, where work is characteristically difficult, slow lacking in splendour and glory, has all too often sought the hitch on to ideas that are fashionable in the opinion of the day. Thus at present, statistics are constantly applied to most of the major questions in therapeutics. Yet in this case statistics are no more than an attempt at application of calculation of probabilities. Let us try to see what opinion we should form*" [50]. They proceed to attack the statistical differences that are so readily apparent in Civiale's database, the fact that most of his patients are older than age 14 whereas most of the lithotomy patients are younger than this age. This makes a statistical evaluation suspect to begin with and they quote, "*these tables also comprise a total of 257 patients treated by lithotripsy, among whom there were only 6 deaths, and among these there were barely 2 or 3 who were under 14*" [50]. They continue in their deliberation with "*The mathematicians who have concerned themselves with the calculation of probabilities have all emphasized the need for the greatest accuracy and care in the classification of facts so as to avoid ill-considered and inaccurate associations which so easily lead to error*" [50]. They come to my favorite part next, "*When our famous Morgagni, with all the power of his genius, equally able to collate facts and to deduce from them the most accurate and judicious conclusions, said:* ***Non numerandae sed perpendendae observations****, one should not count, but rather weigh the facts, he energetically expressed one of the most important conditions attached to the theory of calculation of numerical probabilities applied to medicine*" [50]. To their credit, they did not discount Civiale's presentation and encouraged him to continue, again in their own words, "*The commissioners invite Mr. Civiale to pursue his statistical research to increase the volume of data, and to provide more circumstantial detail to make it more conclusive; at the same time, they are honoured to call for the approval of the Academy for his work*" [50].

Early Modern Trends

Elisha Bartlett (1804–1855) paid attention to the writings and admonitions of Jules Gavarret [52]. In 1844 he wrote about the need to collect large numbers of cases for clinical trials: "*I shall enter into a somewhat detailed exposition of the subject before us…the treatment of disease; for the materials of which I am almost entirely indebted to the admirable treatise of M. Gavarret, on Medical Statistics*" [53]. Others would follow the lead advancing the science of medicine including William Sealy Gosset (1876–1937), Ronald Aylmer Fisher (1890–1962) (Fisher's exact test), Jerzy Neyman (1894–1981) who described confidence intervals in 1934, and Austin Bradford Hill (1897–1991) [54].

Sir Henry Thompson also collected voluminous amounts of data concerning stone-forming patients. Thompson was able to collect 1,827 lithotomy cases (793 from Norwich). He noted that stones were rare in children from well-off parents but were much more common among the lower classes. His age stratification was as follows: below 16 was 13 % hospital and 0.4 % private, 16–50 years of age 27 % hospital and 11.7 % private, age

50–70 was 56 % hospital and 66 % private, and those aged over 70 were 4 % hospital and 21.9 % private [55]. J. Swift Joly compared a series of bladder stone patients operated on from both St. Peter's Hospital and the Mayo Clinic as follows (raw numbers) [56]:

	St. Peter's Hospital	Mayo Clinic
First decade	3	4
Second decade	7	13
Third decade	9	34
Fourth decade	34	59
Fifth decade	48	71
Sixth decade	90	164
Seventh decade	122	183
Eighth decade	54	69
Ninth decade	4	9

It was noted that in France utilizing the Civiale data the trend for the disappearance of bladder stones was also apparent [56]. McCarrison still noted a large number of bladder stones in both India, and Thomson confirmed this in Southeast Asia at the beginning of the twentieth century [57, 58]. For completeness, it is of historical interest that Lonsdale and Mason have used modern microscopic crystallographic and X-ray diffraction methods on this same stone collection to verify that the stones of the children that were presented from the Norfolk and Norwich Hospital are in fact similar to those of endemic disease regions of the world today, such as Thailand, Turkey, and India, which are conclusively associated with poor diet and the formation of ammonium urate stones in the bladder [59, 60].

As the prelude to modern stone epidemiology, this section should end with a bridge from the old to the new, and nicely there is just such a source. Stone disease and bladder stones in particular were declining. Surgical therapies had advanced but what happened to morbidity and mortality? We will now turn our attention to the hybrid American/English author and physician John W. S. Gouley. Gouley was trained in England but practiced and wrote in New York City. His 1873 book entitled Diseases of the Urinary Organs: including Stricture of the Urethra, Affections of the Prostate, and Stone in the Bladder provides us with some intriguing epidemiological information [61]. Gouley is aware of the lithotomy work from the Norwich School, the results by Civiale, as well as those by the contemporaneous British surgeons. He has seen the incorporation of anesthesia and aseptic surgical principles and has reviewed the works of Bigelow and Thompson. He is in a position to tabulate outcomes from many surgeons and centers and provide us with broad statistical comparisons. His first table on surgical outcomes comes on page 319 of his book and compares recent surgical outcomes as follows [61]:

Sir Benjamin Brodie	115 cases	9 deaths	Or, 1 in 12.77
Crichton	122	8	1 in 15.25
Sir Wm. Fergusson	109	12	1 in 9.08
Sir Henry Thompson	204	13	1 in 15.69
Dr. Keith (Aberdeen)	116	7	1 in 16.57
Dr. Ivanchich (Vienna)	100	13	1 in 7.69
Dr. Swallin (Stockholm)	49	7	1 in 7
Dr. Porta (Pavia)	122	24	1 in 5.08
Dr. Gordon Buck (New York)	55	8	1 in 6.87
Aggregate	992	101	1 in 9.82

This represents a remarkable compilation of surgical mortality, though it does not address morbidity. This still was the era before antibiotics so there were more than likely lots of septic complications as well as returns to surgery for missed fragments. But Gouley is not yet finished. He presents a newer perineal approach called Allarton's median lithotomy. He presents the same table for comparison [61]:

American cases	139	5	or, 1 in 27.8
Mr. Allarton's	161	14	1 in 11.5
Norfolk and Norwich Hosp.	64	13	1 in 4.92
Aggregate	364	32	1 in 11.37

Still not done yet, Gouley then goes into some hybrid methods that also evolved using some rather dramatic mechanical devices making a hybrid operation possible combining Allarton's median lithotomy with lithotrity, calling this

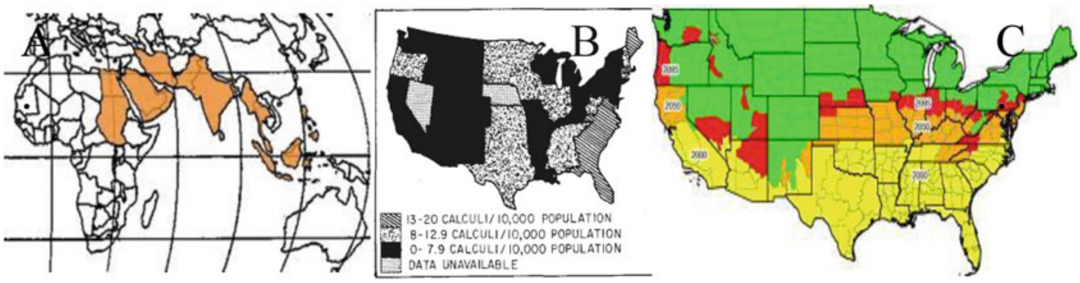


Fig. 24.3 (**a**) The stone belt worldwide. (**b**) The original stone belt described by William H. Boyce, C. current stone belt in the United States

perineal lithotrity. He goes through this technique described initially by Mr. Dobeau from Paris. He concludes with the following, "*My own experience in this operation is limited to three cases, which terminated favorably, and I have no hesitation to recommend it as preferable to median lithotomy with fragmentation of the stone*" [61].

J. Swift Joly was the surgeon at St. Peter's Hospital for Stone in London. On May 23, 1934, he read a paper that summarized the early modern notions of urolithiasis and epidemiology to the annual meeting of the American Urological Association in Atlantic City, N.J [56]. He summarizes rather encyclopedically the knowledge of epidemiology of stone till that time. He goes into details about regional soils as a risk factor but essentially discounts this hypothesis. He also looks at the thought that hard water is a risk factor but again shows that does not hold up to scrutiny. Switzerland with the hardest water in Europe had the lowest incidence of stones, whereas Holland with the softest water had the highest incidence of stones. He noted that though climactic conditions had been implicated, there were discrepancies here such as the Sudan where stones are rare, but thermal extremes are the norm. The single geographical fact that appears to hold is that dairy farming correlated inversely with the prevalence of stone disease. Looking at ethnicity he ranked the Hindus, Arabs, and Southern Chinese as the highest-risk groups in the world (correlates well with the modern world stone belt—Fig. 24.3a). Joly also took a look at religious preferences but noted no significant correlation. He was not sure of what to make of heredity, since living conditions and diet were so closely linked to families. He noted that cystinuria though was definitely familial. He spent the bulk of his talk discussing the implications of diet and the incidence of stone disease. He credited Yelloly as being the first to recognize that even families living in poverty could form uric acid stones stating, "*large employment of ill-fermented farinaceous food was, by the resulting indigestion, a, if not the, cause of the prevalence of the stone in Norfolk*" [56]. He called bladder stones a "*poor man's disease,*" noticing that it had vanished in most of the Western world remaining only in Turkey, India, and Southern China. He specifically discussed milk, "*Milk is purin-free, and contains practically no oxalates. It is, however, a veritable store-house of soluble phosphates*" [56]. He believed this was the reason why children from Western countries had so few endemic bladder stones, because of the cheap availability of milk year-round, which was lacking in Norwich. He did discuss the risk of vitamin deficiency but believed these were rare now in the West. He did warn about the excess of vitamin D causing stone disease and noted that heliotherapy then practiced widely in England did increase stone formation in children with tuberculosis. Cereals, especially unprocessed cereals, correlated highly with the development of stones, especially when they made up a large fraction of diets; here he quoted liberally from the work of McCarrison. One final caveat is worth considering, the risk of infection and the increased risk of stone recurrence was discussed. He noted that Dr. Cuthbert Dukes had isolated a bacterium that might cause stones, called *B. proteus*. He noted that Grossman in von Lichtenberg's clinic claimed to have found infection in 315 out 750 stone recurrences (42 %). He concludes with discussions that Raffin in 1911 noted that pyogenic cocci or *Staphylococcus albus* was frequently associated with stone formers. This was highlighted by the work of Rosenow and Messier. He believed that most calculi are formed in aseptic conditions but more work was necessary [56].

Modern Urolithiasis Epidemiology

Stone disease has long plagued mankind; however, prior to the Industrial Revolution, the bladder was the primary repository of these concretions. In the United States and most developed counties, upper tract stones predominate (97 % in the calyx, pelvis, ureter vs. 3 % in bladder or urethra) [62]. The incidence of stone disease has been estimated at 0.1–0.3 % or 240,000–720,000 people in the United States yearly [63]. 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 [64]. 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). In the United States alone, the prevalence has doubled since 1964–1972. This is not isolated to the United States, however, with Germany, Spain, and Italy also showing increased prevalence. [65] It has 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). This is no longer true with some regions showing parity in gender distributions. 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 United States, and we will discuss the gender issues separately (chapter on Equal Rights) [66, 67].

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 ranks first in the world as the highest incident population with stones and the United States is 17th. Within the United States 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 United States has long been known to be the “stone belt” of this country (Fig. 24.3b, c). 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 [66, 67]. 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 [68]. Following extremely warm and dry temperature swings in the Italy, it has been noted that there is a 1-month window where both the incidence and prevalence of stone disease rise [69].

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 [70]. 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 wages 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 [71]. 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 [71]. There is no longer any question that diet and types of fluid intake affect the incidence and prevalence of urolithiasis [72]. Fructose consumption, cereal grains, carbonated beverages, increased sodium ingestion, amounts of fruits and vegetables, and oxalate intake have all been linked to stone disease, but these studies are complicated to conduct and interpret [73–76]. These findings correlate strongly with the global rise in obesity and the association with increased risk of urolithiasis [77].

Children with urolithiasis present with all of the same stone types and metabolic derangements that afflict the adults, but anatomic variability must be a priority consideration. Both infectious stones and genitourinary tract anomalies are more common in pediatric stone-forming patients than the adult population. The incidence of stone disease in children is 1/1,000–1/7,600 hospital admissions with females and males being effected equally [78]. One rather unique occurrence in children is hematuria associated with hypercalciuria, hyperoxaluria, and hyperuricosuria without an actual calculus [79]. Cystinuria is more likely to present in children than in adults and should be screened if a stone is present. The surgical modalities for treating symptomatic children are the same as with adults. The least invasive modality should be considered first (SWL). The absolute contraindication to this therapy would be an obstructed kidney. Open surgery may be required more often in children than in adults to synchronously correct anatomical aberrations if they coexist with stones.

Pregnancy represents another unique condition where urolithiasis can complicate the normal gestational process. Occurrence during pregnancy is estimated at 0.05–0.35 % and is least common in the first trimester but rises throughout the second and third trimesters [80]. Urolithiasis represents a major differential diagnostic dilemma during pregnancy [81]. A high index of suspicion is necessary and invariably a screening renal ultrasound is performed. Problems with this study are the mechanical and hormonal responses of the patient to her pregnancy with dilation of her upper urinary tracts (especially the right side). Limited intravenous urograms can be obtained limiting the number of exposures especially beyond the first trimester. Women of childbearing age with known asymptomatic renal calculi should consider treatment prior to becoming pregnant [82]. Pregnancy remains a contraindication for SWL. All other modalities remain with palliative diversion by percutaneous nephrostomy or ureteral stenting being the foremost alternatives as there is least risk to both mother and fetus. Approximately 50 % of pregnant patients with urolithiasis will pass them spontaneously during their pregnancy and observation is a definite option. Nonspecific therapy can and should be recommended during the pregnancy by pushing oral fluid and adding citrus fruits four times daily, but restriction of dietary calcium and multivitamins seems unwise. Full evaluation and therapy can proceed following delivery.

Stone disease continues to increase in prevalence in North America and represents a major health-care issue. Urolithiasis represented 0.9 % of discharge diagnoses with a mean hospital stay of 3 days [83]. The cost to the health-care system in 1993 was estimated to be 1.83 billion dollars [83]. If left alone most stone formers will suffer a recurrence and at least 1/5 of these will recur several times. Given the complexity of this disease and the continued recent advances in the medical and surgical therapies, it is not surprising that some medical generalists and specialists defer to a urologist for both evaluation and therapy of stone disease. Even among urologists there are those who prefer to provide only the surgical interventions for this disease and defer the medical management to another. There are centers where both are managed synchronously [84]. Such centers that foster interactions between the surgical and medical therapeutics, that enhance the compliance of both specific and nonspecific therapies, and that investigate the basic pathophysiologic derangements, seeking alternatives with even less risk for patients both medically and surgically, should be utilized [85]. The more complex the stone-forming patient or the more recalcitrant a patient is to metaphylactic measures, the more he/she requires such a center carefully focusing on outcomes. Prior to leaving the topic of urolithiasis, three special scenarios deserve special attention for primary care physicians. Children with stone disease are an exception to the management discussed previously. Dietary changes cannot be as harsh as they are to an adult because of requirements for growth. Pregnant women are another exception because standard radiographic evaluation and surgical interventions must be considered carefully as the fetus carries some risk. Finally, if stone disease itself were not complex already, there is a group of individuals who use this disease for personal benefit, often times seeking intravenous narcotics and will from time to time present to your emergency department called fictitious stone formers (see section on Fictitious Stones).

Discussion

> "*Figures often beguile me, particularly when I have the arranging of them myself; in which case the remark attributed to Disraeli would often apply with justice and force: 'There are three kinds of lies: lies, damned lies and statistics.'*" [86]
>
> —Mark Twain

It is now more than 150 years since Louis and Beddoes wrote their respective works and medicine continues onwards. Medicine has of course evolved; it has grown from largely a home-based provision to now a hospital-based one. Journals of medical science have proliferated at an unprecedented rate; now it is all but impossible for even the Journal of Urology to continue its original mandate propagated by Hugh Hampton Young in his opening editorial. Stone disease has become so complicated that articles appear in many diverse sources making virtually impossible for even a stone expert to keep current, and stone disease is but a fraction of the pathologies within the genitourinary tracts of humans. In 2005 Richard D. William wrote a brief one-page synopsis of the Urologic Diseases in America Project at the urging of the American Urological Association and the National Institute of Diabetes and Digestive and Kidney Diseases; they sought funding for the largest secondary analysis of urological epidemiology ever conducted [87, 88]. Some of this information has become available, especially regarding urolithiasis [89]. But like all bits of information, one must be judicious in the interpretation. The 10–25 % of medical decisions are evidence-based rule coming from a series of conjectures, many of them humorous, starting back in the 1970s. For example, in an exchange between giants of epidemiology, Kerr White and Archie Cochrane in Wellington, NZ, Kerr had just suggested that "*only about 15–20 % of physicians' interventions were supported by objective evidence that they did more good than harm*" *when Archie interrupted him with:* "*Kerr, you're a damned liar! You know it isn't more than 10 %*" [89].

Let's look at another epidemiologic problem in stone disease, the management of patients with staghorn renal stones. Staghorn stones are most often infectious stones, the consequences of infections by urease-producing organisms such as *Proteus mirabilis*. Uric acid and cystine can also form staghorns, but infectious stones consisting of struvite and various calcium phosphate types predominate. An article appeared in the Journal of Urology in May of 1976 essentially stating that even asymptomatic patients with infectious staghorn stones had an overall mortality rate of 28 % during the 10 years of observation in this study. Four patients developed carcinomas in the affected kidney and sixteen developed life-threatening pyonephrosis. They compared this to patients who underwent stone removal and their mortality rate was 7.2 %. [90] Now the problems with the study are obvious; this was a retrospective study and selection bias certainly played a role. But the American Urological Association did make staghorn stone disease the topic of its very first intense investigation for national guidelines [91]. The group did approach the issues raised by Blandy and Singh but state "*Limitations to the process of developing the treatment guidelines became apparent during the Panel's review of the literature. Most obviously, there is no uniform system of categorizing staghorn calculi, no standard method of describing the collecting-system anatomy and no widely utilized system for reporting the size of staghorn calculi. Although the most valid data for a meta-analysis are generated by randomized, prospective studies, only one such study was available for analysis, one more than for the previous guideline project*" [91]. We are left with doing the best we can for these truly ill patients, knowing that there are risks for intervention and risks if no intervention is elected, just as Blandy and Singh noted or perhaps, philosophically speaking like the Civiale Commission in 1835.

Another statistical quagmire is the patients presenting with lower pole renal stones. Since Isaac Newton developed the mathematics explaining gravity, lower pole stones have presented problems, though there is some literary license being taken here. David Murphy and Steven Streem expressed the incidence of lower pole calculi were on the rise secondary to availability of shock wave lithotripters. Fragments were hypothesized to fall into the lower pole, thus serving as a nidus to develop stones in this location [92]. Many if not most lower pole caliceal calculi are asymptomatic. In one of the rare natural history papers, Glowacki and coworkers followed asymptomatic calculi for years with no measurable adverse outcome. They noted that the risk of becoming symptomatic requiring intervention was 10 % per year, with a cumulative 5-year event probability of 48.5 % [93]. The problem with this study was that not all of the patients had lower pole stones. In 2007 a small series of patient with asymptomatic lower pole stones were followed for mean of 52.3 months (range 24–72 months). There were 24 patients (14 males, 10 females) with a mean diameter of 8.8 mm (range 2.0–26.0 mm). Progression in size occurred in 9/27 renal units (three patients had bilateral stones) and they intervened on two of these. Interestingly, no patient needed any intervention prior to 2 years of follow-up [94]. Now we have a randomized trial that should help clarify everything. This study was reported in 2010 and included 94 patients with asymptomatic lower caliceal stones. Thirty-one patients received percutaneous nephrostolithotomy (PCN), 31 received shock wave lithotripsy (SWL), and 32 were simply observed. The mean follow-up was 19.3 months (range 12–29 months). The PCN group was all stone-free at 3 months. The SWL group had only 54.3 % of the patients stone-free, and the observation group had seven patients (18.7 %) required intervention at a median of 22.5 months (range 18–26 months) and one of them (3.1 %) passed the culprit stone without any intervention [95]. Now things get really messy; they did not include ureteroscopic laser lithotripsy into the mix of options which is a perfectly acceptable alternative with also low morbidity. Decisions and outcomes from SWL are highly dependent upon the infundibulum-pelvic angle and other complexities such as the skin to renal distance (obesity makes a difference). Complications are not really mentioned but it appears that the observation arm might have had the fewest. Once again we in need of a lower pole renal calculi study group and guidelines will be forthcoming.

Epidemiology of stone disease is a vast and complex subject with a fascinating historical record. The Académie des Sciences' 1935 response to Jean Civiale's statistics is poignant, "*The detailed study of the causes likely to produce calculi disprove a certain number of statements issued in relation to different foods and some beverages that were too hastily declared likely to cause the disease. Whatever the research taken into consideration, everything remains obscure, there is nothing but uncertainty on this point*" [50]. This statement was made in 1835 and has yet to be adequately addressed, though our methods have improved and our databases have enlarged.

There is always a hidden additional motive that underlies any treatment strategy and that is physician income which we will discuss further in the final chapter of this book. In a rather bold indictment, recent authors have factored this into their stone-free formulas. They conclude with the following statement, "*Finally, we do need a new index, which would be proportional to the SF (stone free) rate and quality of life measurement and inversely proportional to the management costs weighed by procedures' number*" [96]. Now if finances don't heat the arguments over urolithiasis, global warming certainly will, if you believe this skeptical science. But a recent paper in Kidney International projected using computer models that a 10 % rise in the prevalence rate might be expected in the next half century with a corresponding 25 % cost in health-care expenditure [97]. It is appropriate to conclude this chapter with a quote from another history paper notably on Civiale and statistics: "*Introduced in 1992, EBM* [evidence-based medicine] *is defined as the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients* [98]. *EBM cautions against actions based only on experience, expert opinion or extrapolation from basic science. Best evidence is derived from sound clinical research, validated by robust statistics,* *leading to the development of clinical practice guidelines and new treatment paradigms*” [99].

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25 Pathophysiology

Introduction

> "*No calculus is formed without having in addition to its crystalline substance a colloid matrix.*" [1]
>
> —Sir Henry Morris, 1901

The question that has perennially been asked throughout the whole history of urolithiasis is: How do stones form? Researchers also at many times in the past have thought that they had indeed discovered this magic moment. In this chapter we will now pursue the methods that have brought us to our current conceptions. Following the development of knowledge about the chemical composition of the stones themselves, attention was turned to the stone-forming process itself. We have discussed the former in detail under the founding fathers of stone chemistry section. We also began this second part in the chapter on Gray's Anatomy and Liesegang Rings. It is good at this point to recall Mr. Rainey's research in 1858 believing that urinary salts were drawn together and consolidated into the calculus by a force that he called molecular coalescence which appeared distinct from that of simple (though via the physics of crystallization this is" not quite true, see Chap. 17. Rainey had a profound impact on both Henry Vandyke Carter and William Ord who continued his hypothesis for some time [2]. This theory also has some historical roots with John Hunter, who suggested that stone formation might be akin to the development of shells and teeth [3]. Much of their research work was performed in simple in vitro urinary solutions, and they added colloids and salts and developed a rather sophisticated method of imaging the development of stones with microscopic slides, which could be perceived as the forerunner to modern crystallographic methods [4].

But in order to make significant progress in the understanding of the actual pathophysiology inside the kidney, more sophisticated methods were necessary. Minkowski, Ebstein, and a whole host of physiologists would open the floodgates for animal models to develop stone disease [5–9]. Animal models would be augmented by cell culture models for even more detailed physiologic methods. Complex physical chemistry methods would be applied using continuous infusion systems to actually monitor "real-time" crystal dynamics. Animal models would be created that explored the genetic factors affecting stone formation by sophisticated knockout of key genes. All of these techniques have contributed greatly to our increasingly sophisticated understanding of stone formation and progression. Epicenters of investigation have also provided key insights into the actual events leading to Randall's plaques forming which has generated huge new research paradigms in the past decade. The actual mechanisms of stone formation are known to include increased solute filtration and excretion, crystal nucleation, growth, and aggregation of the crystals within or near the renal tubules.

Animal models have been recognized as being essential to the progress of medical science, but there are increasingly vocal critics of these

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methods. In 2005, over 500 scientists signed a public petition supporting the statement "*virtually every medical achievement of the last century has depended directly or indirectly on research with animals*" [10]. This petition included signatures of three Nobel laureates and 250 professors. The study of the causes of a disease is called its etiology. The mechanisms by which the disease causes damage or injury are termed pathogenesis. Understanding these specifics in a disease process is difficult in live human subjects, but the understanding of these specifics is absolutely essential in developing methods of dealing with the disease. Stone disease is a complex interaction of many mechanisms that result in the formation of more than one type of stone. The complexity of stone formation and the interactions between molecular and cellular systems have resulted in a plethora of animal models, cell culture models, physical chemistry models, and now even genetic models to further our understanding of these complex interactions [11]. Nonobstructing stones produce no symptoms or signs other than often causing hematuria. It is only when stones become mobile and impinge in some way on the urinary tract that pain is caused. The colic produced by stones follows typical patterns, but the hallmark feature is pain independent of body position, motion, sleep, or wakefulness often associated with nausea, vomiting, and diaphoresis. This is a historical overview of those investigators and their models which predominately represent a twentieth-century overview.

Light in the Darkness

> "*Men of science learn every day from experience; by experience they constantly correct their scientific ideas, their theories; rectify them, bring them into harmony with more and more facts, and so come nearer and nearer the truth.*" [12]
>
> —Claude Bernard

Most would consider William Harvey's work on circulation to be the founding moments of experimental physiology, but the work was completed years before he published his work in 1628. Marcello Malpighi certainly did pioneering physiologic research on renal models that would lead to much of our discussion that will follow. But some have speculated that the interest in basic pathology and Rudolf Virchow's influence might have ignited the sudden rise in physiologic research [13]. Carl F.W. Ludwig in Germany and Claude Bernard in France certainly seized the moment to develop sophisticated research methods. These studies all appeared synchronously with Charles Darwin's prolific outpouring of work capped with his 1859 *On the Origin of Species* [14]. But Claude Bernard (1813–1878) pioneered many of the advanced physiologic methods that are used in modern medicine and medical physiology to understand health and disease. He became the preparateur for the Collège de France in 1841, and he married Francois Marie Martin (Franny) in 1845. By 1955 he succeeded Magendie as professor at the college, and he became the first chair of physiology at the Sorbonne. Napoleon III built Bernard a full experimental laboratory at the Muséum d'Histoire National before beginning his torment from bladder stones. He believed that his claim to fame was simply that he brought the scientific method to medicine. In 1865 he wrote his famous discourse on scientific medicine called *Introduction to Experimental Medicine* [12]. But his estranged wife, Franny Martin, became increasingly outspoken critic of his use of animals in experiments. And the antivivisection movement certainly became increasingly vocal in his aftermath [15]. Eduard Pflüger and Franciscus Donders also developed physiologic research interests [16].

Bernard is often lauded by today's historian because he was so dedicated to the precise elucidation of complex physiologic mechanism. He stated "*But when we reach the limits of vivisection we have other means of going deeper and dealing with the elementary parts of organisms where the elementary properties of vital phenomena have their seat. We may introduce poisons into the circulation, which carry their specific action to one or another histological unit… Poisons are veritable reagents of life, extremely delicate instruments which dissect vital units*" [12]. He had a somewhat jaded view of the clinical physician, quite probably secondary to the limited treatments that were then available: "*In a word, I consider hospitals only as the entrance to scientific medicine; they are the first field of observation which a physician enters; but the true sanctuary of medical science is a laboratory… In leaving the hospital, a physician…must go into his laboratory*" [12]. In 1889 the first International Congress of Physiology was held in Basle. New journals to rapidly transmit the growing amount of research were started [17]. The Archiv für pathologische Anatomie und Physiologie und für klinische Medizin had been founded by Rudolf Virchow and B. Reinhardt in 1858. Pflüger's Archiv began in 1868, the Journal of Physiology was published in 1878 (Michael Foster), and the American Journal of Physiology started in 1898 [17]. The first significant British experimental physiologist was William Sharpey an accomplished anatomist who became the first Chari of Physiology at University College in 1836. Sharpey taught Michael Foster, C.S. Sherrington, C.G. Douglas, and J.G. Priestley. John Burdon Sanderson, E. G. T. Liddell, and J. S. Haldane all rapidly rose into giants of early experimental physiology [18]. Clinical research laboratories soon became attached to teaching institutions, such as William H. Welch at the Johns Hopkins Medical School. Now all of the pieces were in place to start a true revolution of knowledge, for example, Ivan Pavlov (psychophysiology), Charles Sherrington (neurophysiology), Otto Frank and Ernest Starling (cardiovascular physiology and hormones), Camillo Golgi (neurophysiology), and Richard Bright (renal physiology) [17]. The fathers of modern medicine were all in place, and the ancient malady of urolithiasis awaited for researchers to begin the long uphill battle of unraveling its vast potential.

Morand was a surgeon who famously was sent to London by the French Academy of Sciences to investigate the surgeries of William Cheselden. Morand famously reported back to the Academy that indeed Cheselden had become *the* surgeon in London; he added that he had been particularly struck by the fact in one case upon which Mr. Cheselden operated in his presence the operation was completed in 54 s [19]. M. Morand first reported calcium oxalate stones spontaneously in the Black rat [20]: "*He* [Morand] *informs us that it is much more frequent in males than females; and that almost all Rats, when they become old, have stones in their urinary passages, and swellings and ulcers in the kidneys. In one Rat, M. Morand found twelve stones, of which nine had become the size of coriander seed, and three were smaller. From others he took out stones of the size of a grain of wheat. The composition of these stones was very different from that of stones found in other animals. Instead of having, like those, a somewhat spherical nucleus, serving as a basis to concretions which are formed round it in an infinite number of extremely thin layers, the present had the same composition throughout. Their shape was also different, some of them being oval, and others cubical: and the cubical ones, it is remarked, had always a shining surface*" [20]. The time was ripe to take animal models as the method for further elucidating the complexities of stone disease. Claude Bernard had shown physicians and physiologists the way [20].

Animal Models

> "*The world will not perish for want of wonders, but for want of wonder.*"
>
> —J.B.S. Haldane

A model is an imitation or stand-in for something else; hence, an animal model is a stand-in for the human in a study of disease. Animals have been used since the earliest histories of medicine and science, though their relevance since the time of Claude Bernard has been increasingly questioned. But it is via these models of stone disease that much of our current knowledge of the pathophysiology of stone disease is derived. Animal models for stone formation typically are developed to better study one aspect of the disease process. Different variables can be controlled, and the stone formation can be rapidly investigated. The animals can be sacrificed, and the kidneys and urinary tract can be examined. Blood can be drawn, and micropuncture aspirations of renal tubules can tell almost moment-by-moment changes in the physical chemistry [21].

Rats have been one of the principal animal models utilized, although many other species have been investigated including fruit fly, limpets, guinea pigs, hamsters, otters, rabbits, cats, dogs, and pigs. There are many methods of getting an animal to form stones, though the specific type of stone makes each model unique. Calcium oxalate is the most common type of human stone, so a great deal of animal model physiology has concentrated on this stone type. Rats by far have the experimental animal of choice [22]. The urinary tracts of animals are different than humans and include significant characteristics that make them easier to study. Rats in particular have smaller kidneys, are unipapillate, and have fewer tubules, a simpler pelvis, and smaller urinary spaces [23]. The rat kidney has the same medulla-to-cortex ratio (1:2) since both animals need to conserve water. Human kidneys are on average 12×6×4 cm. whereas rats are 1.6×1.0×0.9 cm. The human kidney weighs about 160–175 g and the rats 0.75–1.2 g. A human kidney has on average 5–6 papillae and the rat only one. The number of nephrons per kidney is 850,000–1,200,000 in humans compared with 30,000–31,000 in rats [23].

M. Tuffier reported as early as 1893 that animals could be induced into forming stones [24]. Oskar Minkowski developed an animal model to induce uric acid stone formation by large doses of adenine in dogs in1898. He noted that the kidneys appeared inflamed after the administration of adenine to the dogs. He could not identify an increase in allantoin which was expected following a load of purines to these animals [5]. But it was a model for stone formation that others could follow and improve upon. Wilhelm Ebstein (1836–1912) was one of the first investigators to develop animal models for urolithiasis using various species [7]. Arthur Nicolaier was his assistant in the laboratory. After feeding the animals he specifically examined their kidneys. First they investigated the use of adenine injected subcutaneously in rats to induce uric acid stone formation. They observed deposits within the kidneys [8]. Ebstein and Nicolaier similarly induce calcium oxalate crystals in the urine by feeding dogs large quantities of soluble oxalates in 1896 and 1897 [8, 9]. He first noted calcium oxalate crystals in the renal tubules of animals as well as systemic toxicities such as muscle spasms and occasionally death [9]. Ebstein and Bendix obtained the same results in rabbits injecting adenine and observing the lagomorphs kidney for uric acid deoposition [9]. Helen Baldwin followed these investigators with another dog model of induced stone formation in 1900 [25]. David L. Macht was an experimental physiologist and pharmacist who began to investigate the pain of stone colic at Johns Hopkins University in the early 1900s. He particularly used porcine models to better understand the ureter's response to pain medications and stones [26].

Lynwood D. Keyser began a study into the formation of stones as his thesis for his medical degree at the University of Minnesota. He went on to work at the Mayo Clinic and continued his animal studies, principally rabbits. He performed multiple studies in his rabbit population, feeding them different types of solutes (sodium bicarbonate, oxalic acid, calcium lactate, calcium oxalate, calcium chloride, calcium lactate, sodium benzoate) via different routes of administration and performing autopsies and quantifying the differences between controls [27]. He expanded his trials to other feedings adding whole cocktails of ingredients trying to induce formation of stones. He performed literally hundreds of experiments upon the rabbits detailing their pathology and urinary microscopic sediments [28]. He also moved on to dog models. He reproduced his dietary methods in the canine model and continued to experiment on the pathophysiology [29]. Keyser was prolific in his early animal investigations which he continued into his practice years. He investigated parathyroid extracts in the formation of stones, developed a model for vitamin A deficiency and stone formation, investigated urea splitting bacteria as a causative etiology, and began some of the first investigations of biofilm formation by bacteria on implanted foreign bodies in the urinary tract [30–32].

Charles Higgins likewise began to develop animal models of stone disease utilizing albino rats at the Cleveland Clinic. He was initially interested in the vitamin A deficiency model [33]. He noted that the mechanism for stone formation was the hyperkeratosis of the urinary epithelium that seemed to promote the formation of alkaline urine, infection, and stone formation [34]. Higgins took his experimental findings one step further. In patients with stones and recurrent stones, he began an experimental regimen of vitamin A supplementation and showed some effect [35].

Miley Wesson, the president of the American Urological Association in 1935, summed up his observations on the applicability of animal models of stone disease to our future care of stone patients in his presidential address [36]. He said, "*We have great hopes of the answer to our problem coming from the work being done at four centers of research. Keyser has for ten years been doing intensive experimental work along the line of etiology and prophylaxis…while Lower and Higgins have almost made the high vitamin acid ash diet a household word*" [36]. He goes on to express the great regard medicine has for animal models of disease, but suggests "*I have decided that we know little more about how to prevent stones than did Hippocrates or Bence-Jones*" [36]. We have come a long way since Wesson comments. Animal models have indeed become a substantive pathway of finding complex interactions of inhibitors and promoters, as models of nephrocalcinosis, to evaluate the complex role of colloids and the electron microscopic effects and locations of early precipitation. Animal models have fundamentally altered our understanding of stone formation [37–39]. All the final frontiers are opening to these models. Cell biologic systems in vitro are beginning to show basic metabolic pathways that are abnormal in stone formation [40]. Even the genetics of stone formation are beginning to be unraveled [41].

Cell Culture Models

In 1665 Robert Hooke described and illustrated the first known cell and the foundation for our modern notions of cell biology began [42]. In 1897 Loeb noticed that blood and connective tissues survived in tubes containing plasma and serum. Ljunggren began to experiment on human skin explants which remained viable in ascitic fluid. In 1902, Gottlieb Haberlandt described the first cell culture in nutrient medium containing glucose, peptone, and different salts. The following year Joly was able to get salamander leukocytes to proliferate in a hanging drop preparation. In 1907 Ross Granville Harrison cultivated amphibian spinal cord using frog lymph clot also using a hanging drop and kept the tissue viable for weeks. Burrows followed with chick embryonic cultures using a chick clot plasma in 1910. M.R. Lewis and W.H. Lewis first attempted to replace natural fluids with an artificial medium in 1911 [43]. Alexis Carrel had already won his Nobel Prize when he developed a composite culture media using blood serum, embryo extract, and saline in a sterilized aseptic flask in 1912 [44]. George Gey, Ward Coffman, and Mary Kubicek derived neutral epithelial cell line from the cervical cancer of Henrietta Lacks, called the HeLa cell line in 1951 [45]. There are believed to be more of Henrietta's cells alive today in cultures, than were originally present in her body when alive [46]. All of this lead to the culture of the Madin-Darby Canine Kidney cell line (MDCK) of distal renal tubular epithelium which were identified in 1958 and characterized in 1966 [47].

Cell culture models enable the investigator to analyze the cellular mechanisms of stone formation without all of the other confounding problems of the in vivo systems. There are now human embryonic kidney epithelial cell lines (HEC-293) that are beginning to be investigated; this is in comparison to the huge amounts of research that has centered upon the canine cell line (MDCK) [44]. Many groups have investigated the cellular mechanisms of calcium transport and the effects of promoters and inhibitors utilizing these cell culture methods [48, 49]. Both calcium and oxalate transport have also been extensively investigated as has been the subcellular morphology in both calcium oxalate and calcium phosphate stone formation [50]. But truly significant work involves the crystal-cell interactions that can be done in vitro with cultured cell lines. It is known that calcium oxalate crystals can bind to renal tubular cells and that this binding depends upon membrane lipid asymmetry, epithelial polarity, membrane fluidity, degree of cell differentiation, the cell type, the presence of macromolecules, and exposure to oxalate [51]. John Lieske and colleagues from the Mayo Clinic have now evolved from the cell culture models into advanced cell biology of pathologic renal calcification and are beginning to unravel the fundamental issues of the origin of calcification itself [52]. We will venture into this territory some in Chaps. 29 and 32.

Chemistry Models

In 1823 John Howship wrote *A Practical Treatise on the Symptoms, Causes, Discrimination and Treatment of Some of the Most Important Complaints That Affect the Secretion and Excretion of the Urine* [53]. He presciently noted that our knowledge of the causative factors of stone formation were incompletely understood. However, he noted "*that any irregularity or excess in diet, a paroxysm of fever, excessive exercise of body and mind, or any other circumstances that induce debility, will occasionally bring it on*" [53]. Howship generalizes a bit from the burgeoning literature on physiology when he notes that "*temporary disturbance of the circulation through the kidneys from fatigue in travelling may derange the functions of these organs without the intervention of stomach or bowels*" [53]. He specifically names this condition as "*stone diatheses*." The hunt for specific chemical pathways was launched, and the clinicians of the twentieth century were up to the task [54]: "*The mystery of stone formation in the human body has engaged the attention of physicians from the earliest dawn of medical history*" [55].

By 1923 the theories of stone formation had become vastly more complex and sophisticated. Spitzer and Hillkowitz reported on the causes of kidney stone formation that supersaturation of the urine with crystalline materials in addition to complex colloid physical chemistry probably represented the etiology [54]. The basics for the colloid chemistry was arising from basic research in Germany from Schade [56]. J. Swift Joly concurred but added a caveat of his own based on some personal surgical experience at St. Peter's Hospital in London. He now believed that the ability of the kidney to clear small stone particles was so good, that there had to be associated with the formation of crystalline deposits, a mechanism for retention of these proto-stones (Randall also would address this consideration) [55]. He hypothesized in 1928 that stones formed predominately in the lower poles of the kidneys [57]. He made this after observing 167 operations for renal stones that eighteen cases had another calculus in a calyx where it could not escape. One of these was in the upper pole, two were in the middle calyx, and 15 were found in lower pole calices [57]. But the new world American academic machines were now in full gear, and Fuller Albright, Alexander Randall, L.D. Keyser, and C.C. Higgins were all entering the stone arena.

Colloids and macromolecules had interested investigators of stone formation since Rainey's dissertation. As biochemistry developed so did the capacity to study these complex molecules and stone disease proved to be a fruitful area of research [58]. William H. Boyce became interested in infections and stone disease and began a systematic research agenda centering upon infectious stones [59]. He became substantially interested in the matrix proteins associated with these stone types. First all stones contain macromolecules so they are clearly significant to our knowledge of stone disease. But struvite stones appear to have the most types of macromolecules than any other stone type [60, 61]. And this was the point of Rainey's work; the syntheses of pearls, shells, coral, and bone all require the orchestration of proteins: "*Some of these direct mineral ions to the construction site, where they fashion them into crystalline building blocks and assemble them into intricate filigrees, weapons, armory and dwellings. Others act as macromolecular scaffolds that become incorporated into the final mineral fabric, imparting rigidity, texture and elasticity*" [62]. Table 25.1 represents a list of the macromolecules that have been detected in stones. Some proteins inhibit stone formation in animal models, in cell cultures, and in crystal systems. Some proteins are mediators of crystal adhesion and internalization within tubular cells [63].

Table 25.1 Macromolecules currently isolated from human stones [62]

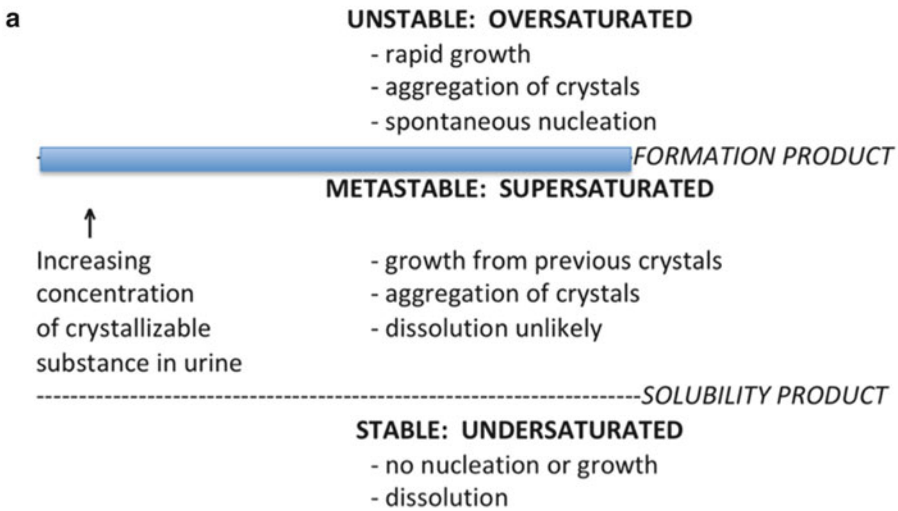
Proteins	
Human serum albumin (HSA)	Alpha and gamma globulins
Tamm-Horsfall glycoprotein (THG)	Nephrocalcin (NC)
Alpha-1-microglobulin	Hemoglobin
Neutrophil elastase	Transferrin
Osteopontin	Alpha-1-antitrypsin
CD59 protein (protectin)	Superoxide dismutase
Beta-2-microglobulin	Alpha-1-acid glycoprotein
Apolipoprotein A1	Retinol-binding protein
Renal lithostathine	Prothrombin fragments 1 and 1+2
Porin	Inter-alpha-trypsin inhibitor chains
Calprotectin (calgranulin)	
Glycosaminoglycans	
Hyaluronan	
Heparin sulfate	

Crystal dynamics and crystal growth chemistry and physics have also burgeoned since our discussions of René Just Haüy (1743–1822) who studied crystal growth, crystal geometry, and the concept of unit cell. Now science is performed with mixed suspension mixed product removal (MSMPR) principles, and they can be fully automated [64]. These crystallization systems revolutionized stone research and our understanding of stone growth, effects by inhibitors and promoters, and aggregation of particulates. Birdwell Finlayson at the University of Florida did some early pioneering work in the field of continuous crystal analysis systems [65]. The group at the Mayo Clinic followed with crystal dynamic studies as well, and a plethora of systems and methods developed [66]. In an attempt to standardize these papers, a call was made to come up with applicable terms that everyone could utilize [67]. Fig 25.1A illustrates the simplified graphic mechanism that has become the standard representation for the physical chemistry of crystallization. There are three zones of saturation; first the undersaturated zone has no ability to form crystals. In the metastable zone, factors can affect the ability of crystals to form. In the supersaturated zone spontaneous nucleation does occur, and crystals can aggregate and grow unless something in the system intervenes or inhibits this process [68]. This method of crystallization of course is dependent upon energy to drive the crystallization process. This is the basis of much of Finlayson's paper from 1978, and the driving force to the kinetics is the concentration of the solute, A_i/A_o [69]. When supersaturation is less than 1, crystals do not form, grow, or aggregate. When supersaturation is greater than 1, crystals can form, grow, and aggregate. The concentration of urine solutes and pH are the main determinates of supersaturation which are also dependent upon urine volume (Fig. 25.1).

Many factors alter the physical chemistry such as amount of urine generated, the aridity of the environment, the urine pH, and the presence or absence of promoters and inhibitors [70]. All of these variables are controllable in the laboratory using crystallization systems. Epitaxy is the oriented overgrowth of one crystalline phase upon another [71]. Uric acid and calcium phosphate can both serve as epitaxial staring points for calcium oxalate precipitation [72]. The early 1970s saw controversy amongst the chemists as to the most significant component of stones, calcium oxalate versus calcium phosphate. Rose suggested that calcium oxalate might be more important because this was the most common mineral at the central cores of most stones. Charlie Pak thought that brushite initiated the growth of stones while Meyer believed that hydroxyapatite seed crystals induced most stones by epitaxially from a metastable supersaturated solution of calcium oxalate [73, 74]. Meyer continued these studies and showed that the process could be reversed with calcium oxalate serving as the seed crystal for brushite [75].

24-h Urine Collections

Crystalluria has been noted since the very first microscopists began to gaze at the urine of stone formers. In fact, early on it was noted that crystalluria followed dietary intake in the 1800s even in



b

$$D = 2\left[\frac{1.62 \cdot A \cdot T}{1440 \cdot 2 \cdot (4/3) \cdot \pi \cdot \rho \cdot B \cdot C}\right]^{1/3}$$

$$= 0.1024\left[\frac{A \cdot T}{\rho \cdot B \cdot C}\right]^{1/3}$$

Fig. 25.1 (**a**) Modern understanding of the states of crystallization, simplified physical chemistry [67] and (**b**) Finlayson's derived fixed particle formula [85]

non-stone formers. The presence of crystals in the urine is a first requirement for the formation of stones since they represent the building blocks upon which stones are built. Robertson and colleagues were the first to note that stone formers tended to have aggregates of calcium oxalate crystals in their urines versus non-stone formers who had small groups of crystals [76]. This data has not been effectively collaborated, and Robertson's original patient group was small and confined to an inpatient metabolic unit. Urine collections however hold the keys to understanding the physical chemistry of crystallization, nucleation, and aggregation because of the concentration of the solutes or crystal ions. Many methods including timed collection, spot urine samples, and full 24-h urine collections have been employed over the years, but the 24-h urine studies have become the standard. Reuben Flocks identified an association of hypercalciuria and stone formation in 1939at the University of Iowa [77].

Fuller Albright used 24 urine collections in his primordial studies investigating hyperparathyroid patients at the Massachusetts General Hospital and also noted a group of non-parathyroid patients with elevated urine calcium levels [78]. They called this group idiopathic hypercalciuria because they had no known mechanism to explain this phenomenon. Rose was a consultant chemical pathologist at St. Peter's Hospital for Stone and became interested in stone disease and urinary chemistry, and he tried to quantify and define the normal limits of urinary calcium [79]. He noted an evolution in the urine chemistries themselves with improvement in the accuracy of methods to identify and quantify both calcium and oxalate in urine samples. But in reviewing multiple definitions derived from either 24-h urine collections or timed urine collections, including ratios of calcium/creatinine, there was no real overlap between these derived definitions themselves leading to marked uncertainties in the diagnosis using older methods [80]. Curhan and colleagues also noted the problem with definitions in an epidemiologic cohort [81]. Pak was quick to point out that the problem of definition has to be carefully controlled by dietary or exogenous influences [82].

Complex chemistry evaluation on the urine of stone formers had by necessity to await sophisticated chemical methods of evaluation to evolve. An experimental group from Leeds, England, and one from Dallas reported sentinel findings in 1968 and 1969 that confirmed the preliminary findings of Albright and Flocks. Timed urine collections had become the gold standard for evaluating the excretion of urinary solutes that could be measured with increasingly sophisticated accuracy. Robertson would go on to make the assertion that the oxalate ion concentrations were much more critical than the calcium concentration.

Birdwell Finlayson and EQUIL

Birdwell Finlayson (1932–1988) was one of the iconic figures of modern stone disease science who died suddenly of an idiopathic hypertrophic cardiomyopathy on July 22, 1988. Birdwell was born and raised a Mormon in rural Pocatello Bannock, Idaho, by parents Birdwell and Jessie Leone Smith. He attended Idaho State College from 1950 till 1953 and completed his premedical studies at the University of Utah. He attended medical school at the University of Chicago in 1957 and residency there until 1961 [83]. He performed a postgraduate fellowship with Dr. C.W. Vermeulen and became profoundly interested in urolithiasis [84]. He continued to acquire knowledge and remained at Chicago earning a Ph.D. in biophysics in 1967. His thesis was on the kinetics of formation and dissociation between actin and myosin [83]. Finlayson joined the faculty at the University of Florida in 1967 and became full professor in 1973. He was referred to as "Bird" by those colleagues who knew and worked with him. He was athletic and an accomplished downhill skier [83]. He was a licensed pilot and flight instructor; he was an aerobatic stunt pilot and loved to ride his skateboard around the University of Florida's campus. But his interest in stone disease was legendary, and his contributions to modern stone science were broad and significant [83].

Upon his arrival at the University of Florida, Finlayson helped form the Kidney Stone Research Center there and attracted colleagues of like-minded interests. This unit became one of the epicenter sites for funding fundamental research into urolithiasis by the National Institutes of Health as a Special Center of Research Excellence [83]. In 1976, Birdwell derived the classic equation proving that the urinary tract defenses were such that a fixed particle must be the source of stones, a landmark article in urolithiasis (Fig 25.1B.) [85]. He begins this article as follows "*Because of the experimental difficulties in investigating the site of initiation of stone disease, very little concerning detailed mechanisms of this disease have been written*" [85]. He goes on to quote scientific methods of investigation that are essential to the development of modern theories quoting one of his professors from the University of Chicago, John J. Platt's "Strong Inference" work in some detail. These concepts are essential to understanding Finlayson's objectives [86]. They have their historical foundations in approaching every scientific problem that harken back to the Francis Bacon's original methods that were articulated by William Whewell, John Herschel, and Charles Babbage and lead to the foundation of the British

Association for the Advancement of Science [87]. First devise alternative hypotheses, next devise crucial experiments (or several of them) to exclude one or more of the hypotheses, third carry out each experiment so as to get reproducible (clean) results, and fourth recycle the experiments to formulate sub-hypotheses or sequential hypotheses to refine the work and the questions. It is Finlayson's first reference in his work and became the guiding light of the remainder of his career [88]. Finlayson doubted the validity of Alexander Randall's findings noting that Randall's plaques were just too common in the non-stone-forming population. He did promote the research into finding the mechanism of crystal adherence in the renal tubules and thought that this would be a urinary protein product. In his conclusions he noted "*Calculations suggest that free particles cannot grow fast enough to cause stone disease in the upper urinary tract. However, free particle stone disease seems quite feasible in the case of male children with small urethras and adult males with large residual urines*" [85].

Another major contribution of Birdwell Finlayson was in the area of crystallization and the theories of supersaturation. Ion product equations are easily calculated for simple fluids; however, urine is an extremely complex biologic fluid with a water base. There are many ions in solutions of urine which make calculation of ion products to get supersaturation values very complex mathematically. It was Finlayson who wrote a computer program using a Fortran IV computer that was able to first solve these equations, making it a tool in evaluating a patient's 24-h urine relative supersaturation. He named the program EQUIL [89]. He also collaborated with others to write a BASIC language general program that could be widely utilized about 10 years later [90]. This accomplishment led to the ability of laboratories to place the results of 24-h urine collections into readily perceived risks of stone formation utilizing relative supersaturations. Now for the first time, clinical scenarios could be evaluated relatively painlessly, and the urines of stone-forming patients could be followed and feedback given on how well they were accomplishing hydration, or dietary limitations, or medical therapy in even complex stone-forming scenarios. Our abilities to predict somewhat accurately the stone risks of patients were derived from the complex integration of formulae necessary to calculate relative supersaturation that began with Birdwell Finlayson. Charlie Pak was one of the original investigators who initially tried to measure the relative supersaturation of calcium oxalate in the urine of controls and stone formers [91]. It is fitting that Pak would eventually follow up on this area of stone research and develop an improved method of computer-derived method of determining relative supersaturation. The Joint Expert Speciation System was compared to EQUIL 2 and proved to be significantly more accurate than the older computer algorithms in calcium oxalate saturation [92].

Bird was interested in every aspect of urolithiasis except perhaps the history. He was interested in physical chemistry; he first defined the pKa of uric acid [93]. He was interested in infectious stone disease and the protein matrix in such stones. He was interested in the processes of crystallization and pioneered autoanalyzers to investigate crystal growth, aggregation, and nucleation. He was also interested in calcium phosphate stones and their physical chemistry. He was a pioneer investigator and one of the first six institutions in the United States to work with Christian Chaussy bringing shock wave lithotripsy to Florida. A Dornier HM-3 lithotripter was installed in August 1984 at the University of Florida. He presented some of the early work on the physics of the lithotriptor, working on spark plug life and patient outcomes and risks. Finlayson helped pioneer new technologies for treating his stone patients, developing a method for retrograde intrarenal access for percutaneous nephrostomy as well as a ureteral access system for ureteroscopy [94]. He was one of the first centers in the United States to formally begin to train fellows in stone disease with several of these continuing his legacy after his untimely death at age 55 [83]. His research unit continued to generate significant amounts of basic scientific research well after his demise.

In Chap. 29 we are going to discuss the events and collaborative efforts that have brought us to our current state of knowledge regarding urolithiasis and the histories of a group of like-minded, diverse scientists and clinicians that began to cooperate in research strategies in the 1980s called the *R*esearch *O*n *C*alculous *K*inetics Society. Birdwell Finlayson was also integral in the formation of this entity which survives today and strongly continues in the tradition and pathways initially founded by him. It is a fitting tribute to Dr. Finlayson that the Society is as strong and dynamic as ever, and its members continue at the forefront of cutting edge of stone disease investigation [95].

Discussion

> "*Any hypothesis regarding the etiology of stone, or indeed of any disease, must be in accordance with all the known facts concerning it. A theory that runs counter to any one fact must be abandoned, while one that is in complete agreement with our present day knowledge may be found wanting in the fuller light of tomorrow. Its place then will be on the scrap heap.*" [57]
>
> J. Swift Joly, 1934

All stone types have similar pathways in their formation and growth, despite the myriad of conditions that are the underlying cause. The history of scientific investigation as to the cascade of events that leads to the initial lesion within the kidney, subsequent growth, and the pathology associated with stones has been the focus of much of the twentieth-century science. This has involved development of rather sophisticated models in animals, in cell culture, and in chemistry systems. Currently even human kidneys have provided a renaissance of scientific interests in stone disease by sophisticated biopsy and scientific investigations of human Randall's plaque investigation at numerous centers, and we will talk more about this in Chap. 29. The understanding of the pathophysiology is beginning to be unraveled, and the potential for truly understanding the complex nuances of this disease is realistic. All of the current work however is based upon the studies of past investigators and nowhere is this so clearly evident than in the original investigations by Alexander Randall. The proof of the concept that the pathophysiology is beginning to be understood would be the appearance of effective treatment strategies and medications to minimize the risk of stone development itself. It is fitting to conclude this chapter with just such a historical consideration.

There were no scientifically proven methods for treating patients with recurrent stone disease prior to the twentieth century that improved upon the recommendation of the Hippocratic physicians. Diet and fluids were generally advised. During the early part of the twentieth century, basic research was making progress, such that vitamin A and an acid ash diet were becoming recommended [96]. The very first medical therapy was to lower phosphate excretion which would have slightly helped patients suffering from phosphate-containing stones, which are a minority [97]. Alkalization helped also a small group of pure uric acid stone formers and slightly helped those unfortunate few that suffered from cystine stone disease [98]. Now chemistry and physiology had begun to point to new pathways of therapy. When diet and fluids were not enough then there were drugs now that might help. Thiazide diuretics were found to lower urinary calcium by direct action on renal tubules and may be used for long periods of time for this purpose [99]. Sodium cellulose phosphate lowers urinary calcium (and magnesium) by exchanging dietary calcium for sodium in the gastrointestinal tract and may also be used for long periods of time, but this is rarely used today [100]. Inorganic phosphate may be administered in the form of one of its sodium/potassium/hydrogen salts [101]. Most investigators today believe that phosphates have little merit in treating stone patients [102]. Magnesium oxide also appears to have an ability to reduce crystallization of calcium oxalate and calcium phosphate in low doses [103]. An entirely different therapeutic approach is the use of allopurinol to lower urinary urate which can predispose to calcium-containing stones by a variety of mechanisms [104]. Finally there is the potassium alkali medications; potassium citrate and potassium-magnesium citrate are also effective in managing patients with hypocitraturic calcium oxalate as well as uric acid stone formers [105, 106].

Sakhaee in a recent review article summarizes much of our knowledge about the pharmacology of stone disease prevention, quoting much of the randomized, placebo-controlled trials that have been performed [107]: "*It has been increasingly recognized that the spectrum of the presentation of nephrolithiasis is wide, and it may be characterized as an acute, localized, chronic, or systemic illness. It has been shown that nephrolithiasis may be associated with an increased risk of end-stage renal disease, coronary artery disease, the metabolic syndrome, hypertension, and diabetes mellitus. Therefore, targeted pharmacologic treatments are imperative in the management of this disorder*" [107].

Patients should also be advised to restrict the intake of oxalate-rich foods, and if Robertson et al. (1976) are correct, this is more important than restricting calcium intake. Urinary oxalate varies with season of the year presumably because certain oxalate-rich foods are seasonal, e.g., beetroot, spinach, nuts, rhubarb, and strawberries, and undoubtedly these foods should be restricted. Calcium stone formers usually have higher oxalate excretion on 24 urines than non-stone-forming controls, and ascorbic acid and high-protein intake make this phenomenon worse. Calcium taken orally actually binds intestinal oxalate, thus decreasing its absorbance and probably explains at least part of the problem of the inadequacy of limiting dietary calcium intake [108]. Patients should be advised to increase fluid intake to at least two liters daily and reduce sodium ingestion to 2,300 mg (100 mEq) daily. Dietary restriction of protein should also be generally recommended to 0.8 to 1 g/kg/day as these have shown efficacy in the randomized trials. Finally, calcium ingestion should not be reduced but should be supplied by foods rather than supplements in calcium stone formers [109]. Understanding and research into the pathophysiology of urolithiasis has paid substantial dividends in this past century. Available are general and specific methods to control and prevent this disease, yet the prevalence has continued to increase substantially in the past 30 years. Despite the relative differences between various stone types and the multitude of aggravating conditions, the pathophysiology of stone formation might just be capable of being tamed, controlled, and overcome.

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26 The Rarest Stone of All!

Introduction

> "*I cannot forgo this opportunity to stress how undesirable it is for surgeons to seal up calculi in glass phials without investigating their chemical composition*." [1]
>
> —Alexander Marcet, 1817

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 counties, upper tract stones predominate (97 % in the calyx, pelvis, ureter vs. 3 % in bladder or urethra) [2]. The incidence of stone disease has been estimated at 0.1–0.3 % or 240,000–720,000 people in the USA yearly [3]. 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 [3]. 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). With so many people and so many stones formed, it should surprise no one that rare varieties will occasionally be found. This is a historical investigation into the rare varieties of urolithiasis with specific attention placed upon the rarest type of all.

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 [4, 5]. 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) [6, 7]. 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 [8–10]. In this same population, newer protease inhibitors such as indinavir have been increasingly associated with stone formation [11]. 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 [12]. Other drugs have also rarely been reported to precipitate out into clinically significant stones including the following: ciprofloxacin, guaifenesin/ephedrine, and phenazopyridine [13, 14].

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 [15]. The reported solubility of xanthine at pH of 5 is known to be 50 mg/L (compared to 150 mg/L for uric acid) [16]. In one

M.E. Moran, *Urolithiasis: A Comprehensive History*, DOI 10.1007/978-1-4614-8196-6_26,

study, only 30–40 % of patients with xanthinuria formed radiolucent stones [17]. Screening laboratory studies indicate that the most common finding is a serum uric acid below 2 mg/dL or < 119 μmol/L. In the USA, the incidence of xanthinuria is not known, but from 1 in 6,000 to 1 in 69,000 has been suggested. Both types have been reported with similar distribution [18]. More common, but still rare, is the iatrogenic induction of xanthinuria by allopurinol administration. In particular, uric acid overproduction in patients with Lesch-Nyhan syndrome or those with partial HGPRT deficiency can lead to overproduction of the oxypurines, xanthine, and hypoxanthine [19]. Normally during allopurinol administration, the plasma levels of oxypurines remain between 0.5 and 2.0 mg/dL, well below the solubility limits. Patients with overproduction as noted earlier and some patients with myeloproliferative disorders can result in elevated levels of xanthine above this limit [20]. The disease has been described in virtually all parts of the world now but appears to be less frequent in the USA currently [21, 22]. The disease was first described by Kelley and colleagues in 1968 [23]. Stones are seen in these patients only because of the poor solubility of 2,8-DHA. Calculus formation and crystal nephropathy are primarily seen in children with this disease, but adults can develop stones [24–26]. 2,8-Dihydroxyadenine stones give a false-positive reaction to the colorimetric analysis for uric acid stones. Thus, infrared spectroscopy or X-ray diffraction analysis of these stones is mandatory. These stones are typically radiolucent making the differential diagnosis any of the purine-containing stone possible, but as with uric acid stones, there are exceptions [27]. These patients tend to be well clinically; they do present with recurrent urolithiasis and occasionally crystal-induced nephropathy with no systemic symptoms of gout. This nephropathy can be very significant as demonstrated by a case of recurrent stones following a successful kidney transplant 23 years later [28]. Despite the absent or decreased APRT activity, adenine can be catabolized to 8-DHA and 2,8-DHA making it a far different clinical problem than its counterpart salvage enzyme deficiency (GPRT) inducing the Lesch-Nyhan syndrome.

All of these are rare stone types, but it is time to start tracking down perhaps the rarest of all stones. It is an intriguing tale that deserves a place in a comprehensive history of urolithiasis. The stone we are about to track has not been reported in the recent past; we must search the historical archives to find it, and its history is as fascinating as the enigmatic stone itself.

Searching for the Needle in a Haystack

In the early literature of chemical investigations of urolithiasis, there is mention of a rare blue urinary calculous, indigo. Sir William Osler, the father of modern American medical education and the professor of Medicine at Johns Hopkins University (1890–1905), published the standard medical textbook in the beginning of the twentieth century, The Principles and Practice of Medicine. Osler was widely regarded as the physician's physician, and his humor and pranks were widely known. It is not generally known that he suffered from renal stone disease, most likely uric acid nephrolithiasis [29]. His perceptions on a wide variety of medical disease processes reflect his extensive background in pathology and a uniquely inquisitive temperament [30].

In his first edition of the Principles, Osler clearly identifies a rare type of stone afflicting humans as "*indigo*" [31]. Very little information was given, and little to no modern literature exists to substantiate his claim. Several questions arise in this regard. Where does this organic pigment fit into urinary stone disease? There is no modern mention of indigo in kidney stones from the 1940s onwards. Calls to North American stone analysis laboratories reveal no indigo stones in their databases [32]. Prien specifically mentions indigo stones as extremely rare [2]. Osler clearly indicates that this stone is rare, but where does he get this information and is it accurate? Also, is there any modern justification for the formation of this stone? [32].

The musings of the fathers of medicine must always be taken in the context of their writing. It is doubtful that Osler was playing a prank regarding the indigo stone in his textbook. He is known to have perpetrated such pranks in other medical literature using the nom de plume, Egerton Y. Davis (ex US Army), but the serious tone of his textbook cannot be minimized [33, 34]. Even Harvey Cushing mentioned Dr. Osler's statement that indican has occasionally been found in calculi [35]. In addition to reading Osler's *Principles* with particular emphasis on his comments on indicanuria and indigo calculi, we reviewed the history of blue pigmentation, scrutinized Index Medicus, culled modern stone laboratory's databases, and read early urology textbooks in an effort to investigate Osler's claims of a blue urinary stone [32].

The Index Medicus was searched from 1920 backwards to its inception in 1879 for the following subject headings: calculous disease and indicanuria. There are two references on the use of indigo as a cathartic. Twelve textbooks of urology prior to 1940 were reviewed for indigo calculi and indicanuria [32]. Where references were present, each was tracked via the bibliography. Finally, all references from the indicanuria literature were checked for the mention of blue calculi or organic blue urinary stones. Using this search method, four references were capable of being retrieved that directly indicate implicate the rare presentation in humans of a rare blue urinary calculous.

Blue Stones and Blue Urine

The twelve urologic textbooks prior to 1940 had only three references to indigo stones. Herman's *The Practice of Urology* in 1938 stated "*calculi containing indigo are rare*." There is no reference for this statement. In Eisendrath and Rolnick's *Textbook of Urology for Students and Practitioners* (1928), they note that "*Indigo bladder stones are very rare*" [36]. They also do not cite any references for these mysterious blue vesical concretions. The most significant reference in the textbooks comes from White's *Stone in the Urinary Tract* (1929) [37]. He states that "*Indigo is a substance which has given rise to one of the rarest kinds of kidney stones*" [37]. He does not discuss the pathogenesis, associated conditions, or case findings. He does, however, reference a case report that was eluded earlier in Pfister's paper by Dr. Forbes in Philadelphia [38].

The Index Medicus has one published report on indigo bladder stones, from Egyptian mummy autopsies [38]. Pfister's paper was dated *24 years after* Osler's textbook. The stones were analyzed chemically and were indigo blue (vs. indigo red) [39]. References in this manuscript include research work on indigo by Dr. Charles in Edinburgh and Dr. Virchow in Berlin. Osler has known ties to both and has been noted in his biographies to have spent time at both of these centers. In addition, Pfister cites another case report from America of a patient with an indigo calculus (more on this later) [38].

The indicanuria literature before Osler's textbook was lively [40–42]. Theories of the etiology of blue urine included metabolic process via enzymatic synthesis, infections with indigo-producing bacteria (principally from colonic infections), and possible ingestion of materials resulting in indigo excretion. In one particularly poignant medical article, Montgomery in 1908, discussing a patient with indicanuria, specifically references Osler "*speaking on indicanuria*" [43]. In Osler's textbook, section X on anomalies of urinary secretion, he has a subsection on indicanuria. He lists all of the known etiologies for voiding blue urine and concludes by noting that indican has "*occasionally been found in calculi*" [31].

The Rarest Stone of All!

The first reported case was patient of undetermined age that died of an abdominal sarcoma with an obstructed left kidney [44]. Within the obstructed, hydronephrotic left kidney was a branched stone consisting predominately of calcium phosphate and some uric acid in a branching staghorn pattern. In the patient's nonobstructed right kidney, there was noted a small "*blackish cake*"-type stone measuring "*7/8 inches long, 9/16 broad, and 1/10 thick, in shape and look not unlike one of the fruit-lozenges used as vehicles for throat medicines*" [44]. This stone, in the nonobstructed kidney, draws his utmost interest because of the rare nature of the chemical properties of the stone. He notes, "*In colour, it is partly dark-brown, in parts black; the black surface finely granular, but taking a polish when rubbed with the thumb nail. It is of the consistence of a very fine hard chalk or slate. Although the surface looks friable, the substance is very firm, and the section is polished by the saw as it traverses the interior with some difficulty. The hard central part is blue-grey, and does not mark paper. There is no concentric lamination or nucleus*" [44]. He had noted that the stone arrived wrapped in paper and where it "*was noticed to make a blackish-blue mark on paper*" [44]. He did detailed chemical and microscopic analysis upon the stone and its crystals (details of his methods are similar to that in Fig. 26.1) [45]. The stone appeared to be struvite with blood and predominately indigo blue with traces of indigo red. In Ord's own words, "*Reviewing the examination, the conclusions to be arrived at are: that the calculus consists of a matrix of phosphate of lime and magnesia, with a little remains of blood clot; that this matrix is everywhere interpreted by indigo blue, with a little indigo red; and that indigo blue has been deposited in large proportion as an incrustation*" [44]. He then proceeds in the remainder of the article to speculate on the origins of the indigo in this patient's stone. The patient was given creosote [creosote] we learn for vomiting prior to his death; this being an "indigogenous *material*." He hypothesized that bowel obstruction, infection, or a primary metabolic pathway could have caused the indigo stone to form in this unfortunate patient.

Some details are again warranted on this second very unusual and rare case of stone disease because this second case report represents the last known instance of an indigo calculus ever reported. On May 30, 1894, Dr. Forbes from the Jefferson Medical College presented a paper at the American Surgical Association in Washington, DC [46]. The case involved the findings of a postmortem examination of a 27-year-old male suicide victim at Jefferson Medical College. He was 5 ft. 9 in. in height and 150 lb, and we know nothing about the method of suicide or his mental issues. Forbes does indicate however that he had talked to family members who indicate that the deceased never suffered from colic or complained of flank pains. During the autopsy, a mass was noted involving the patient's left kidney (Fig. 26.2.). In Dr. Forbes's words, "*the left kidney surrounded by thick fibrous mass, involving the entire perinephric fat. This inflammatory deposit also involved the blood-vessels passing to and from the kidney. The renal vein was much constricted in passing through the inflammatory mass. The ureter was bound by fibrous bands that slightly compressed it*" [46]. A calculus was present involving the entire pelvis and one calix: "*Professor W. M. L. Coplin, of Jefferson Medical College, made the post-mortem examination and handed me the kidney, with the calculus in situ. The specimen, of which an actual representation is here given, weighs 147 grains; it greatest thickness, for and aft, is 19/32 of an inch. It measures from A to B 1 1/3 inch, and from C to D 1 ½ inch*" [46]. He goes on to discuss his first impressions from this most unusual stone: "*The dark-brown color caused me to think that it was formed of indigo, and drawing it across white paper it left a rough, blue mark, so that I was further impressed that it was perhaps indigo*" [45]. Detailed chemical analysis of this stone indicated that its composition was indigo blue. In the discussion of this case, Dr. Forbes cites another case from London, by Dr. Ord in 1879 [44]. The article concluded by stating that this stone is preserved in the Jefferson Museum [46].

The Thomas Jefferson Medical College has changed dramatically since the late 1800s. The medical museum no longer exists, and many if not most of the pathologic and anatomic exhibits are missing. Michael Angelo is the current TJU Archivist. He is aware of this

On Heating the Powder on Platinum Foil, It				
Does not burn	The powder when treated with HCl	Does not effervesce — The gently-heated powder with HCl — The powder when moistened with a little KOH	Abundant ammonia. The powder dissolves in acetic acid or HCl. This solution gives a crystalline precipitate with ammonia	"Triple phosphate" (mixed with unknown amount of earthy phosphate).
			No ammonia or, at least, only traces of ammonia. Powder dissolves in acetic acid or HCl. This solution is precipitated by ammonia (amorphous)	Bone-earth (magnesium and calcium phosphate).
		Does not effervesce — The gently-heated powder with HCl	Effervesces	Calcium oxalate.
			Effervesces	Calcium carbonate.
Does burn	With flame		Flame yellow, continuous. Odor of burnt feathers. Insoluble in alcohol and ether. Soluble in KOH with heat. Precipitated herefrom by acetic acid and generation of H_2S	Fibrin.
			Flame yellow, pale, continuous. Odor of resin or shellac on burning. Powder soluble in alcohol and ether	Urostealith.
			Flame pale blue, burns a short time. Peculiar sharp odor. The powder dissolves in ammonia, and six-sided plates separate on the spontaneous evaporation of the ammonia	Cystin.
	Without flame		Does not give murexid test. The powder dissolves in HNO_3 without effervescence. The dried yellow residue becomes orange with alkali, beautiful red on warming	Xanthin.
		The powder gives the murexid test — The powder when treated with KOH gives	Strong ammonia reaction	Ammonium urate.
			No noticeable ammonia reaction	Uric acid.

Fig. 26.1 The chemical analysis schema that would have been followed by both Dr. Ord and Dr. Forbes in evaluating the potential indigo stones. The missing piece of chemistry to identify indigo would be the color test with sulfuric acid that would make a clear, blue fluid. Also the sooty odor when heated upon the platinum foil is also characteristic of indigo [45]

case report and has found the original steel engravings used to make the illustrations for Dr. Forbes's article and has kindly lent us a high-definition image for this work (Fig. 26.2 Thomas Jefferson University, MS19, box4, ff6) [32].

Discussion

Osler's *The Principles and Practice of Medicine* was first published when he was 41 years old while he was the new professor of medicine and

Fig. 26.2 The Forbes's article original steel plate for illustration taken with permission from the Thomas Jefferson Medical College. (Letters were used for size references in the original text). This is the last documented case report of an indigo calculus in the world, 1894 [46]

the physician-in-chief at the Johns Hopkins University in 1892. The textbook's widespread popularity and durability through seven personalized editions attest to *Principles* significance [47]. Osler introduced a method of discussing diseases, which has subsequently been adopted by many other medical authors. He began each section by defining the disease, introducing a brief historical note, discussions, etiologies, transmission (for known infectious diseases), morbid anatomy, symptoms, diagnosis, prognosis, prophylaxis, and treatment. Cushing once remarked: "*Some one*, *some day*, *could well write a volume devoted to a study of the successive editions of this famous work which continues to exercise an enormous influence on students of medicine*" [35]. In the chapter on renal disease, Osler defines urolithiasis as "*the formation in the kidney or in its pelvis of concretions by the deposition of certain solid constituents of the urine*" [31]. His sections on the etiology and pathology are still correct by modern standards. In his discussion of the chemical varieties of calculi, he classifies certain rare forms. In this he includes cystine, xanthine, carbonate of lime, *indigo*, and urostealith [31]. It is this mention of a rare organic blue stone that drew our attention since there is no modern recognition of this type of concretion and making it the rarest type of urolithiasis of all!

Indigo is an ancient, organic blue pigment known for centuries [12]. The Romans first became aware of this blue pigment from the Celts who painted themselves (hence Picts) with blue dye derived from the woad plant [48]. Far East trade in the dye derived from the *Indigofera* plant arose next. The monopolization of this blue dye trade led to the British indenturing of the Indian tenant farmers. This prompted a little-known lawyer to intercede on their behalf with the British authorities in 1915 (first name Mohandas—only later Mahatma = honorific Gandhi). By 1830 a German chemist, named Bunge, identified within the byproduct of steel production, coal tar, which were rich in carbon compounds. His students, Kekulé and Baeyer, later synthesized several related benzene ring-containing compounds. Baeyer identified the chemical structure of indigo, synthesized it commercially, and won the Nobel Prize for chemistry in 1905 [49]. The ability to produce indigo pigments from a cheap source such as coal tar undermined the international trade in indigo [48].

Dr. Osler's perceptions of urolithiasis are accurate. The reference in the first edition of *The Principles and Practice of Medicine* to rare indigo calculi is correct [31]. Three reports, two of which were most likely known to Osler, can be identified. Osler's extensive reading, cataloging of medical knowledge, and traveling allowed him to become familiar with these rare medical cases. Urologic textbooks dated from after the publication of Osler's "*Principles*" continue to reference his writings on the rare blue concretions. The mention of this rare blue stone is the feature that prompted this historical investigation. Prien and Frondel continued into the modern era of stone identification to mention the possibility of indigo blue kidney stones [2]: "*Chronology*, *so the saying goes is the last refuge of the feeble minded and the only resort for historians*" [50].

Osler passed numerous stones during his lifetime, but only one while still at the Johns Hopkins University [51]. This occurred after the publication of his textbook. The story of his first bout of renal colic is preserved in one of his resident's case reports (Futcher, 1949) [29]. His subsequent musings on stone passage occur during his later career while Regius Professor of Medicine at Oxford (1905–1919) [51]. He expected but apparently did not confirm that his stones were made of uric acid. His autopsy is significant for noting "*pinpoints of urates*" studding his kidneys [52]. In his *Principles*, Osler can be quoted on the clinical varieties of calculi. He states that uric acid stones are "*by far the most important*" [31]. He might be predicting his own affliction in suffering from these recurrences, half a lifetime before the disease manifested itself.

The possibility that Osler's reference to indigo calculi could be a prank, though possible, is unlikely. During Osler's first stone episode, Futcher (1949) indicates that Osler tried to give him a pebble from his walkway, perhaps trying to impress his junior colleague with the size of a stone that the "Professor" could pass. Futcher correctly concluded that the stone was quartzite [29]. This case is perhaps the first documented fictitious urinary stone. Osler's other publicized urologic prank has been previously presented to the American Osler Society by Dr. Earl Nation. The case involved an unusual type of vaginal spasm wherein the partner's penis became captured: *penis captivus* [33]. Osler expressed some degree of remorse for the printing of this trifle [34]. Given the review of the literature regarding indigo, its chemical nature, and Osler's interests in indicanuria, his comments on the rarity of human affliction with blue stones appear to be accurate. Osler probably did not know the significance of King George III's blue urine though it is more than likely he was aware of the medical cause of his madness [53]. Hence, the mystery of the blue stone is not contrived or imaginary but one of those medical rarities that has not been seen now for almost a century. The old professor's breadth of knowledge continues to intrigue those of us who still find impressive a master's method.

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27 The Largest Stone of All!

Introduction

> "*I feel…an ardent desire to see knowledge so disseminated through the mass of mankind that it may…reach even the extremes of society: beggars and kings*." [1]
>
> (Thomas Jefferson-1808 Am. Philosophical Society)

What is it about something odd or setting records that humanity finds so fascinating? Itinerant lithotomists would make a name for themselves by displaying large collections of stones that they had removed from patients. Some would have a large sack filled with the stones that they would allow to be "hefted" or handled by the crowds that they would provide the days entertainment during lithotomies. On May 4, 1951, Sir Hugh Beaver became involved in the question of which was the fastest game bird in Europe; Beaver being the director of Guinness Breweries had the wherewithal to get to the answer and the process evolved in hiring twins Norris and Ross McWhirter to compile what became *The Guinness Book of Records* in August of 1954. There are inherent problems defining records as we will see, but the official website states, "*We do not accept any claims for beauty as it is not objectively measurable*" [2]. The Guinness Book of Records opened a museum in 1976 in the Empire State Building but closed in 1995, perhaps but not likely a world record for opening and closing of a world's record museum. The Guinness World Records 2013 was released on September 11, 2012 [1]. As of August 2006 Canadian Donald Winfield has passed the most kidney stones, $n = 5{,}704$. The reported largest number of stones removed at once was 728 upon Mangilal Jia of India on January 27, 2004 [2].

Also the first major effort from an American author includes Samuel D. Gross's "*Practical Treatise on the Diseases, Injuries, and Malformations of the Urinary Bladder, the Prostate Gland, and the Urethra*" in 1851 [3]. Samuel D. Gross is the surgeon that was immortalized by Thomas Eakins' "The Gross Clinic" painting of 1875. Gross was a pioneering experimental surgeon who rose in fame at the frontier school the Louisville Medical Institute. He practiced surgery there for 16 years before he was lured back to Philadelphia as the professor of surgery at Jefferson Medical College [4]: "*…The consideration of the weight of urinary concretions is necessarily connected with that of their volume. In general, this does not exceed a few drachms or ounces. Out of every one hundred calculi, as they occur in the cabinets of different institutions, or of private individuals, few will be found to weigh more than five or six drachms. One of the smallest ever removed by lithotomy, weighed only ten grains; the operator was Mr. Martineaue, of England, and the patient a boy, thirteen years old. In one of my own cases, that of a boy, six years of age, the weight of the calculus was only five grains. Many examples, however, are recorded of four, six, eight, ten, twelve, fifteen, and even sixteen ounces. Instances of eighteen, nineteen, and twenty*

M.E. Moran, *Urolithiasis: A Comprehensive History*, DOI 10.1007/978-1-4614-8196-6_27,

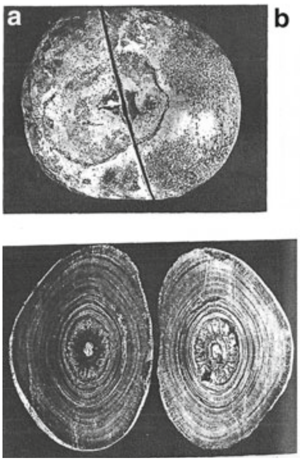
ounces, are related by Borellus, Lusitanus, Cheselden, Pauw, Foschini, Wrisberg, and Sandifort. Fabricius Hildanus describes a calculus which weighed twenty-two ounces, and was four inches and a half in length, by three and a half in breadth. Examples of from twenty-four to thirty ounces are recorded by Deschamps, Pauw, Paget, Tolet, Williams, King, and other authors. In the case mentioned by the latter (London Medical and Physical J 1828), the patient, who was forty-six years of age, had suffered from his infancy, and the stone was seven inches and a half long, by fifteen inches in circumference. Several instances exist in which the concretion weighed thirty-five, forty, forty-five, and even fifty ounces. Mr Henry Earle (London Medico-Chir Trans, vol. xi. p82), of London, has published the particulars of a calculus which weighed forty-four ounces, and was sixteen inches in circumference. It was impossible to break it, and the operator was compelled to leave his task unfinished. Deschamps gives a case of fifty-one ounces; Verdue, one of three pounds three ounces; and Kesselring (Commer Liter Norimb 1739 hebd 9) one of upwards to six pounds" (p. 175) [3].

Howard Kelly was also keenly interested in large stones and records. He notes that Israel described a "*stone was 17 cm. long and 9 cm. in circumference. Rovsing states that he has had stones weighing 148 grains. Johnsen reports a stone of 14.1 cm. long; its longest circumference 33.5 cm., its smallest circumference 28.5 cm. The stone weighed 339 gr. J. Ramsay records a very large stone, and refers to the case of T.R. Jessop, where the stone weighed over 11 ounces; he also quotes Pohl as removing at post-mortem a stone weighing five pounds*" [5].

Largest Historical Stone

Let's turn to the most famous large stone from history and discuss its rather remarkable journey and story. William Heberden is famous as the first physician to describe angina; he is also the uncle of William Hyde Wollaston, one of the founding fathers of stone chemistry. Let's begin with the opening of William Heberden's paper to the Royal Society on this stone in 1750 [6]: "*There is preserved in the Library of Trinity-College in Cambridge, a Stone taken from a human Bladder, which for its uncommon Size, may deserve the Notice of* [*t*]*his, Society. It is of an oval Shape, flatted on one Side and its Surface is smooth. The specific Gravity plainly shews, that danit is of an animal Origin; for its Weight is to that of Water only as 1,75 to 1*" [6]. Heberden takes some pains to produce a litany of eye witnesses who can testify as to the true nature of this unusual case listing Right Rev. Dr. Claggett, bishop of Exeter, the Rev. Dr. Baker, and the son-in-law of the patient who died with this stone. Again in his own words, "*From their Accounts it appear'd, that this Stone was taken from the Wife of Thomas Raisin, Locksmith in Bury, after her Death, by Mr. Gutteridge, a Surgeon, of Norwich* (Fig. 27.1a)" [6]. He recounts Mrs. Raisin's suffering and symptoms noting that surprisingly she suffered little. Again back to his account, "…*and might probably have liv'd much longer with it, if she had not thought herself well enough to attempt a Journey on Horseback; for, while she was riding, she was suddenly seized with violent Pains, that obliged her to be taken off the Horse immediately; After which she could never make Water, unless the Stone was first moved, and she continued in great Agonies till she died*" [6]. He relates that part of the stone had been chipped off to show this curiosity to King Charles II, "*to shew the King that it consisted of various Coats formed one over another, as animal Stone usually do*" [6]. He proceeded to discuss the size and appearance of this stone: "*This monstrous Stone weighs 33 Ounces 3 Drachms and 36 Grains, Troy Weight*" [6]. He believed that about half an ounce had been broken off and stated that another in Paris is reputed to weigh 34 Paris ounces, "*Dr. Lister, in his Journey to Paris, p. 232 which he says was taken from a Monk A.D. 1690 and weighs 51 Ounces*" [6].

Raymond Williamson was able to track down the source of the "*Monk's Stone*" [7]. Martin Lister account was written in 1699 and he actually wrote the following: "*Another popular Disease here is the Stone; and there are Men well*



b

Fig. 1. Exterior of the Calculus; the size of the Original.
A. B. The line of section.
Fig. 2. Section of the Calculus.
a. Lithic nucleus.
b. Oxalate of lime.
c. Ditto, mixed with sparkling triple crystals.
d. Triple crystals with a little lithic.
e. Lithic, with minute layers of fusible Calculus.
f. Triple crystals, (four thin layers).
g. Lithic.
h. Fusible.

	Inches.
Largest circumference	15.
Circumference of the section	13.1
Least circumference	11.7
Weight after being sawn, (exclusive of the dust)	32 oz. 7 dr.
Specific gravity	1.756
Ditto, after being two days in water	1.768

Fig. 27.1 (**a**) Mrs. Raisin's stone removed postmortem by the lithotomist Mr. Gutteridge (*Note*: the chunk missing was probably from being dropped by King Charles II's mistress). (**b**) The findings of J. Cummings' analyses

practiced in the Cutting for it. There are also two Hospitals, where great numbers are cut yearly, as La Charité, and Hotel-Dieu; in both these are Wired Chests full of stones cut from Human Bodies; and in the Chest of La Charite is one, which exceeds all belief; it was cut from a Monk, who died in the very Operation; it is as big as a Child's Head. It is but the Model Pattern of the Stone which is kept in the Chest; which has this Inscription on it:

> *Figure etgrosseur de la pierre, pesant 51 ounces, qui sont trois livres trois ounces, qui a esté tireé dans cet Hospital au mois de Juin 1690, et que l' on conserve dans le Couvent de la Charitè*" [7].

Lister completed his tale of the wonders of the stones of Paris by describing the operation of Frere Jacques, the famous lithotomist whom he observed while in Paris.

J. Cumming was the next person to examine Mrs. Raisin's stone [8]. Cummings describes Mrs. Raisin's stone as follows: "*Its structure is such as, taken conjointly with its magnitude, to make it, perhaps the most curious and instructive calculus in this kingdom; since it presents the characters of not less than four distinct species. The nucleus is lithic, to this succeeds a considerable portion of the oxalate of lime variety, this is followed by layers of the triple crystals, covered by thick coating of lithic, which is occasionally broken by a layer of triple crystals, and the external surface is principally composed of the fusible calculus. – Its present weigh, after being sawed is 32 oz. 7 dr; the specific gravity is 1.756 which after being two days in water became 1.768. It measures 15 inches in circumference in one direction, and 13 ½ inches in another*" [8] (Fig. 27.1b).

King Charles II whom we've met previously in our discussion of quack remedies for urolithiasis was visiting the Newmarket races in 1662 and was shown the current curiosity which was this same stone weighing over two pounds removed from a woman in Bury St. Edmunds. The stone was cut across to show the king the annular internal structure, Liesegang's rings [9]. There are anecdotal reports that the King tried to surprise his mistress, singer Nell Gwynn, by plopping it in her lap. She responded by screaming and dropping the stone breaking off the first piece.

Another very large bladder stone is also described by Sir James Earle in the Philosophical Transactions of 1809 [10]. This stone weighed 44 troy ounces and measured 16 in. around the long axis and 14 in. about the short axis. This stone was housed in the Museum of the Royal College of Surgeons and was lost with the entire stone collection in the fire of 1941. Mr. Clive was the surgeon who tried to remove this stone, but little information persists about the surgery or the patient other than what was noted in the Catalogue of Calculi [11].

Largest Bladder Stone

It is time to return again to Alexander Randall. On March 22, 1920, Dr. E.E. Keiser presented an unusual case to the Philadelphia Genito-Urinary Society [12]. Randall was allowed to present this same case to the American Urological Association later that same week. We will discover during Randall's written description of this stone that he had the capacity to do significant historical research, and he should have been aware of Henle's description of papillary stones as well as Crosse's description as we previously discussed. But this is a chapter on large stones, so let's move to his description: "*Giant calculi in the present day of surgery are so rarely seen that one expects such only from some distant civilization or under extraordinary circumstances*" [12]. He presented a 61 year old male who developed gross hematuria and constipation in July of 1919. Dr. W.H. Morrison performed a roentgenologic examination that "*showed an immense shadow filling the entire true pelvis and extending three finger breadths above the line of sacral promontory*" [12]. He presented in such a weakened condition; they tried to improve his condition prior to undergoing surgery on August 11, 1919. A suprapubic cystotomy was performed and the calculus was removed intact with repair of the bladder, yet the patient died 36 h following this surgery: "*The stone weighed on delivery in its moist state exactly 64 ounces, or 4 pounds; at present it weighs 56 ounces, or 3 ½ pounds. Its longitudinal circumference measures 48 cm. and its greatest horizontal circumference (that above the brim of the pelvis), 40 cm*" [12] (Fig. 27.2a). Now Randall would proceed to discuss the history of the largest stones noting that Keiser's patient is the largest stone to present in situ while still alive; all of the larger stones were noted postmortem. He lists the recent literature first, including Dr. Mitchell's 1915 case of a 30-oz stone and Dr. Emerson C. Smith's 1919 case that was 38½ ounces, and then lists Sir Henry Thompson's Catalogue of Collection, The Royal College of Surgeons Catalogue, and Freyer, Coulson, and Ebstein's cases, noting that none of them exceed 51 oz [12].

He turned to two stones that were larger than "*my specimen*," though it was actually Dr. Keiser's [12]. The first case referred to a stone described by George Louis Le Clerc, Comte Buffon that stated that a stone of 6 lb had been removed, but he meticulously reviews all of Buffon's writings, which are voluminous, and is unable to corroborate this stone as human but

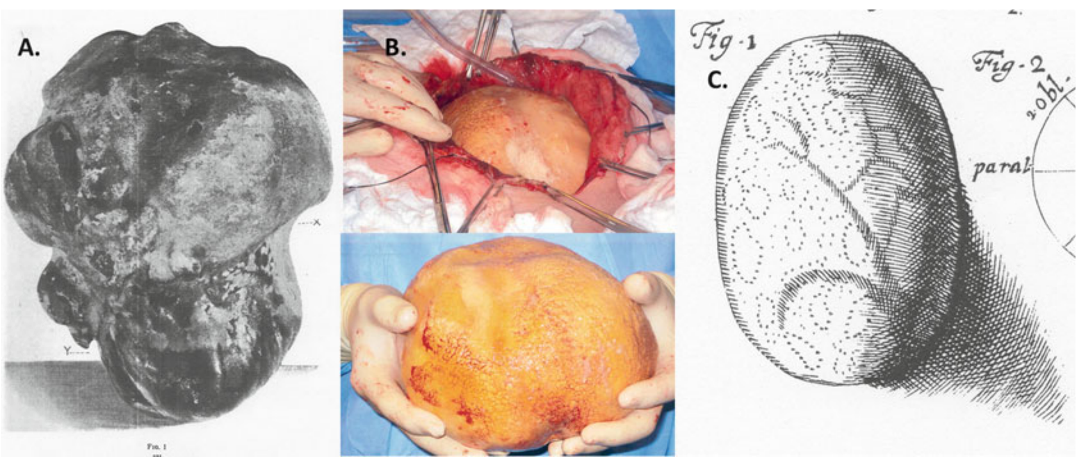


Fig. 27.2 (**a**) Alexander Randall's giant bladder stone, removed in Philadelphia on August 11, 1919 (64 oz., 48 cm. circumference). (**b**) 10-lb stone from ileal neobladder (photos courtesy of Dr. Tim Roddy). (**c**) Thomas Molyneux's famous extraction transurethrally from Sarah Jones, aged 12, on October 16, 1698

might be an animal bezoar. The second case is that of Sir Jonathan Hutchinson who cites that Morand had seen another stone removed post-mortem that was also 6 lb. Sauveur-Francois Morand was a French lithotomist who wrote a book on the high operation (suprapubic cystotomy) in 1729, and he again after reviewing all of his writings "*contains no mention of such a giant calculus*, *nor anything to exceed in size my specimen*" [12]. It may suffice to see from his concluding comments that he believes he has the world's record: "*My conclusions following this painstaking search of the literature*, *are that this represents the largest specimen of human vesical calculus formation of authentic record*, *certainly the largest removed during the life of its host and a specimen so unique that it will probably stand in a class by itself for all time*" [12].

Largest Stone in Urinary Diversion

The urinary bladder is a muscular reservoir that is capable of holding a moderate amount of urine and able to eliminate this product at some appropriate future moment. When the bladder is no longer functional or when some disease condition causes the bladder to become a threat to the life of the patient, then the bladder is now capable of being eliminated and a new reservoir or conduit can be surgically constructed [13]. There are some basic types of urinary reservoirs, simply put as continent or incontinent. The continent types of reservoirs include heterotopic (moved to someplace other than the urinary tract) and orthotopic (moving the reservoir back to the urethra). These reservoirs are both capable of serving as a nidus for stone formation. The incontinent types of reservoirs are dominated by a single type of diversion, called an ileal conduit. This is a simple segment of small bowel (usually the ileum) that is brought out through the abdominal wall with the ureters reattached to the distal end of this conduit that empties into a wearable appliance (most common type is called a Bricker loop, named after Dr. Eugene M. Bricker from Washington University in St. Louis who first performed this type of urinary diversion in 1941 [14]. The ileal conduit typically does not represent a reservoir that stones form because it empties into a drainage bag, but the urinary tract is more prone to infections and infectious-type stones, struvite.

If the patient with a urinary diversion is carefully monitored in their postoperative period if they develop urolithiasis, these can be tackled when they are small. But like so much in medicine, if the conduit is not monitored, then the stone can both form and progress to truly impressive sizes. One such stone presented to an urologist in practice in Mountlake Terrace in Washington State in 2010. A 71 year old male had a radical cystectomy with a continent orthotopic diversion in 1990. This was connected to his urethra and he failed to return for any kind of follow-up after his drainage tubes and stents had been removed in the routine postoperative period. So 9 years later, he presented to a hospital in Everett, WA, with severe malnutrition, bilateral DVTs, bilateral pleural effusions, cirrhotic ascites, liver dysfunction, and a solitary functioning kidney with two distal ureteral calculi, the other kidney just a shell with hydronephrosis and a large stone in his orthotopic bladder. He was transferred to a larger hospital center with specialist to remove the large neobladder stone. This neobladder stone was massive on CT scan and filled his entire pelvis. After stabilization this stone was removed via a suprapubic neo-vesicolithotomy with the weight of the stone being 160 oz (10 lb! Fig. 27.2b). The stone was essentially struvite. He has improved enough that the ureteral stones have been removed as well, but of course he has failed subsequent follow-up visits.

Largest Transurethral Stone

Thomas Molyneux (1661–1733) was an Irish physician and surgeon who was educated at Trinity College in Dublin where he earned his medical degree at age 22. He traveled to London and the Continent and was interested in many areas of scientific endeavor. He was admitted as a fellow to the Royal Society on November 3, 1686, and he contributed greatly over the years. Before telling his tale about stones, he is famous today in reporting the fossilized remains of the great Irish Elk. Sadly, he got both wrong however; the animal was not an elk and it probably did not naturally occur or come from Ireland. In 1698 he wrote a case report with an illustration of a large stone removed from the bladder of a 12-year-old girl transurethrally by dilation (Fig. 27.2c) [15]: "*By one lately performed in this Town on a Girl, between Eleven and Twelve Years Old, on Sarah Jones, that for Six Years past, has been severely afflicted with all the painful and unusual Symptoms of the Stone, but on the 16th of October, was happily relieved, by only dilating gently, the Neck of the Bladder, and then extracting a Stone of a very considerable bulk, without making any Incision at all.*" He continues on, "*The whole Operation was performed in Six of Seven Minutes, and was the more remarkable on the Account of the extraordinary large Size of the Stone, whose Shape and Bigness is exactly represented in the annext Figure, Vid.Tab.Fig.I…By the Size of this we have here figured, it appears to have been so big, that it may seem almost incredible a Solid of that Bulk, should be forced through the Urethra of so small and so Young a Child, without any manner of Section: and that the Child should recover so as to be perfectly well, without the least ill Accident succeeding the Operation*" [15].

Famous Kidney Stones

The archer of Meudon or Bagnolet is the most famous kidney/ureteral stone in history, because, if true, it the first successfully removed upper tract stone on a patient in history. Part of the problem is that the resources that document this case are not terribly reliable though it appears that one of the early family members of the Collots might have been involved with this case, perhaps Germain Collot who lived at the time of Louis XI: "*The doctors of the Faculty of Medicine in Paris, having learned that an archer from Bagnolet, who had been affected a long time by stone had been condemned to death for his crime, petitioned the king and the magistrates to kindly deliver him into their hands in order to prove on him if the kidneys could be opened for removal of the stone without depriving him of his life. The operation was so successful that the man survived for many years afterwards in excellent health*" [16]. This was recorded to have occurred in January of 1474; the archer was arrested for theft from the church in Meudon: "*As it was known that he was much troubled by stone, colic, and pains in the side and that many and divers persons were grievously molested and tormented in a like manner, the physicians and surgeons of the City of Paris, where he was to be hanged, petitioned the King, 'that it would be very useful to see the places where these maladies are concreted, and that this could best be done by vivisecting a human being, which could be well effected on the person of said archer, who also about to suffer death.' This was accordingly done and 'the place of said maladies having been sought out and examined, his bowels were replaced and he was sewn up again.' He was perfectly healed within a fortnight, and received a free pardon*" [17]. This story has morphed over time; one surgical historian fully discounts the renal surgery and believes they were performing a suprapubic or high bladder stone surgery. Nutton and Nutton believe the story to be more mythological, but again there is no true information to take a stand on the actual event [18].

The word "pope" comes from the Greek word for father. The senior priests and bishops of the early Roman Catholic Church were a relatively democratic bunch until about the fifth century, where the bishop of Rome became to be called the pope. Following the eighth century he was exclusively called the Pope. In one recent study of papal health and illness, a table of age, periods of service, and cause of death has been tabulated in Acta Theologica [19]. It is documented that monks, members of the clergy, priests, and the members of the Vatican were better fed, clothed, and sheltered than most of the rest of the people throughout the Dark Ages. In order to become the Vicar of Christ, the individual usually had to rise in the Roman Catholic Church hierarchy and have typically been older individuals. But in earlier times the life expectancy probably influenced the papal selection process, called the Conclave.

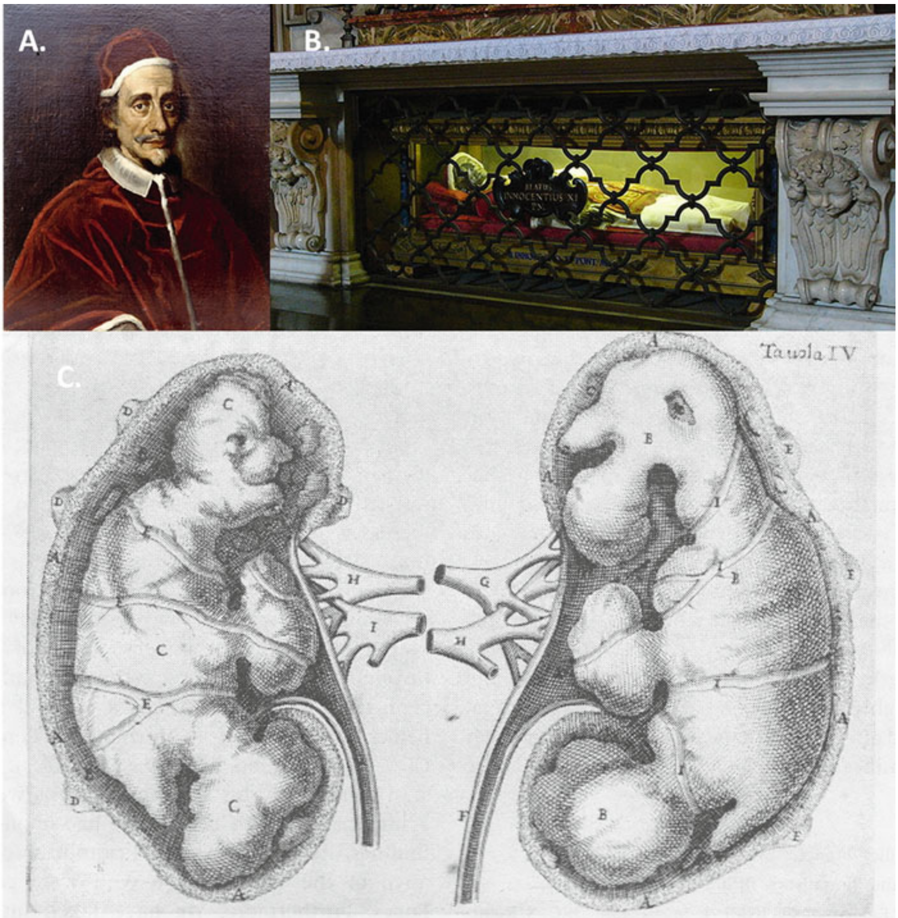


Fig. 27.3 (**a**) Pope Innocent XI, a portrait of the pontiff. (**b**) Photograph of Saint Innocent lying in glass sarcophagus. (**c**) Drawing by Lodovico Sergarili of the autopsy of Lancisi

In the Roman era, life expectancy was 25 and arose to about 35 during the Middle Ages. Between 605 and 1054 the average age of a Pope was 39.3. In the late Middle Ages from 1055 to 1492, it was 59.1. From the Renaissance to 2005, this age was up to 63.9 years old. All totaled, there were 263 Popes in this study, five of whom had terminal renal ailments and several suffered from bladder stones [19]. Pope Innocent XI was born in 1611 as Benedetto Odescalchi in Como to a wealthy banking/trading family from Genoa. He became the Pope on September 21, 1676, turbulent times for the Church with tensions from France and Louis XIV (Fig. 27.3a). Innocent was a robust man of 66 when he ascended the throne of Peter, though as early as 1676 he seemed to have had symptoms of kidney trouble. In fact, he may have sought care from Jean Marie Lancisi, a young physician who may have prescribed something for stone disease. His health was affected by his excessive fasting and the cares of his office, which caused sleepless nights, thus seriously taxing his strength. The attacks of gout, these were nondescript pains commonly attributed to gout but might well have been colic, began in 1682 and continued until his death, which often confined him to his bed. His conditioned worsened in July of 1689, and only his physician and his confessor were allowed to visit with him. It is recorded he prayed before he died, "*O God*, *increase my pains*, *but give me patience*" [19] (Fig. 27.3b). He died on August 12, 1689, at the ripe old age of 79, and there appears to have been an autopsy performed by his physician, Lancisi, and a sketch of both kidneys was performed by Lodovico Sergarili showing massive bilateral full staghorn stones (Fig. 27.3c). The stones were enormous weighing a hefty 7 oz each. In the last little interesting piece of trivia surrounding this papal case of urolithiasis comes from the French side. Jacques-Bénigne Bossuet (September 27, 1627–April 12, 1704) was the bishop in Meaux who was Louis XIV tutor as a child and who was widely recognized for his oratory prowess. He too developed severe kidney stone disease that likewise killed him in 2 years of suffering in 1704 [20].

Smallest, Most Famous Stone

It is worth our while here to recall the case of Stephen Pollard one final time. At about 1 p.m. on Tuesday, March 18, 1828, a previously healthy patient by the name of Stephen Pollard presented himself to the operating table at Guy's Hospital [21]. Pollard was a family man with a wife and five children from Sussex, and at age 53 he was suffering from a bladder stone. Bladder stones are painful, and patients often presented themselves to the mercy of surgeons with the obvious dilemma of continued pain versus the exquisite agony of the surgical procedure itself. Most lithotomies were over in minutes; in fact, until the case of Pollard's, no stone surgery at Guy's Hospital had lasted for more than 30 min. But a young surgeon Bransby Cooper who was Sir Astley Cooper's nephew was doing this case. Bransby Cooper panicked during this routine surgery and is believed to have injured the rectum in the process. The surgery lasted an agonizing 55 min in front of 200 spectators. A friend of Sir Astley Cooper and editor of the new medical journal, The Lancet, railed at the ineptitude of the young surgeon in print. Supposedly the increasing horror of the frantic surgeon caused even the seasoned surgeons in the crowd to leave the hall. Mr. Pollard cried out in agony "*Oh! Let it go! Pray, let it keep in!*" [21] Cooper called out to those remaining in the crowd that "*It's a very deep perineum. I can't reach the bladder with my finger*" [21]. He called for his assistant to raise his hand to see if his fingers were longer. He finally found the bladder and removed the culprit. This token of endurance resides rather inconspicuously in the Gordon Museum at Guy's Hospital, about 3 cm across. Pollard died the following morning and an autopsy was performed. This revealed that he sadly did not have a deep perineum and Thomas Wakley reported to enraptured readers of The Lancet that in issues 239 and 240 he recounted the disastrous surgery from eye witness accounts [22]. One headline read "*Guy's Hospital. The operation of lithotomy by Mr. Bransby Cooper which lasted nearly one hour!*" [22] Bransby Cooper sued The Lancet for libel and sought £2,000.46. The trial made headline news about the quality and standards for practicing complex surgery. Astley Cooper who was called to give evidence regarding his nephew stated, "*I think he is already a very good surgeon, but I do not think he is a perfectly good surgeon. Give him time. Do not crush him at the outset of his career*" [22]. William Dalrymple (1772–1847) had performed ninety lithotomies over his 27-year career as staff at the hospital and was widely regarded as a lithotomist. Dalrymple's reputation was such that he was called to testify for a surgical defendant at Guy's Hospital in 1828; Bransby Cooper whom he stated was an able surgeon. The jury in 1828 awarded the suit to Bransby Cooper, but only for £100. It is fitting that Dr. Thomas Wakley had raised funds for his defense that exceeded this amount which he gave to the widow Pollard and her children [23].

The Fastest Lithotomy

We have presented the life and work of William Cheselden in this textbook on several occasions, because he was the surgeon who worked out the details of the lateral method of Frère Jacques and taught the rest of the world. For a brief period of time, in terms of the overall history of urolithiasis and lithotomy, his method with slight variations became the standard technique. Others have been documented to have mastered this technique such as the brothers Douglas who lived and recorded Cheselden's accomplishments and John became his avowed enemy. But there is no question that his technical prowess at this surgery was beyond anyone else's. He did not stand on his own laurels, and it is recorded in no manuscript that this historian can find that Cheselden ever claimed to be the fastest lithotomist. His total focus appears to always have been upon his patients and performing at his best on every occasion. Morand, the great French surgeon and lithotomist, who came to London to study with Cheselden gave a eulogy after his death. He stated, "*he learnt his anatomy from the celebrated Cowper with whom he resided*" [24]. Morand was disconcerted about the mortality rate of the lithotomy patient in Paris and decided to visit with Cheselden. It appears that there was a significant mutual admiration between the two. Morand repaid the complement by having Cheselden elected to the Royal Academy of Surgeons. Morand recounted the friendliness of Cheselden and related how he was given an instrument, probably the gorget he used during lithotomy, "*et qui foroit honneur au cabinet d'un souverain, puisque l'historier de cette operation tiendra toujours a cell de l'esprit humaine*" [24]. That said however, there are good eyewitness accounts that have documented that he had performed a perineal lateral lithotomy in 54 s, Morand being one. Morand wrote to the French Academy of Sciences during his stay in London that Cheselden had acquired such a reputation that he had become *the* surgeon; then he added the famous notation, and he had particularly struck by the fact that in one case upon which Cheselden operated in his presence the operation was completed in 54 s. There are other competing lithotomists who were quick, but there is no definite proof that they even came close to this stunning technical achievement of Cheselden.

With the discovery and rapid improvement of anesthesia, with the introduction of sterile or aseptic technique of Lister, the need for speed in surgery has rapidly lost both its allure and luster. In fact, the necessity of speed in surgery today leads most young surgeons to view these records to some extent as incompetence. This is certainly not the case with Cheselden's 54-s lithotomy. There was minimal anesthesia and poor analgesia and the significant risk of postoperative death was palpable. No one during his career would have an "*elective*" lithotomy.

Self-Performed Perineal Vesicolithotomy?

No discussion of medical or surgical treatment during the Renaissance would be complete without mention of one curious case that clearly points to an unbelievable act of desperation. The story was originally in the works of the famous anatomist/surgeon Dr. Tulp (made immortal by Rembrandt) (Fig. 27.3) [25]: "*Joannes Lethaeus, a Smith, a courageous man, and very astute, who had already been treated twice by a stonecutter, desired so little to be treated a third time by such a man among his daily trials and repeated slayings, that he decided any wild adventure was more attractive to him than subjecting himself to the knife of the stonecutter ever again. Convincing himself that his health could only improve, and having decided that no one but himself would cut into his flesh, he sent his wife to the fish market, which she didn't mind doing. Only letting his brother help him, he instructed him to pull aside his scrotum while he grabbed the stone in his left hand and cut bravely in the perineum with a knife he had secretly prepared, and by standing again and again managed to make the wound long enough to allow the stone to pass. To get the stone out was more difficult, and he had to stick two fingers into the wound on either side to remove it with leveraged force, and it finally popped out of hiding with an explosive noise and tearing of the bladder*" [26].

> "*Now the more courageous than careful operation was completed, and the enemy that had declared war on him was safely on the ground, he sent for a healer who sewed up the two sides of the wound together, and the opening that he had cut himself, and properly bound it up; the flesh of which grew so happily that there was no small hope of health, but the wound was too big, and the bladder too torn, not to have ulcers forming*" [26].

"*But this stone weighing 4 ounces and the size of a hen's egg was a wonder how it came out with the help of one hand, without the proper tools, and then from the patient himself, whose greatest help was courage and impatience embedded in a truly impenetrable faith which caused a brave deed as none other. So was he no less than those whose deeds are related in the old scriptures. Sometimes daring helps when reason doesn't*" [26]. What extraordinary determination and fortitude it must have taken to drive this man to such an act of self-inflicted desperation.

Self-Performed Nephrolithotomy?

There is a case in realm of kidney stone disease that just might one-up de Doot's surgical endeavor. This case was described anonymously in the Philosophical Transaction in 1695–1697: "*He seems either not to have met with, or not to have believed that extraordinary Case in Cœlius Rhodiginus var. lect. L. 3.c.12 of a Woman, who having for a good while been afflicted with a load and pain in the Region of her Kidneys; scratched with that rage and impatience so long with her Nails, till she made a Wound so large and deep, as to discharge eighteen Stone magnitudine quanta in tefferis visitor*" [26]. This case has no evidence that it actually occurred other than its report in the proceedings of the Royal Society, which does not add to the veracity of this case. But if true, it would be extraordinary indeed.

The First Documented Renal Stone Surgery

We have previously discussed the fascinating tale of the English Consul of Venice who went to the famous Paduan surgeon, Marchetti, to explore his kidney because of his intolerable pains. There was a reliable witness, Charles Barnard who wrote a rather detailed description of the events that is worth recounting:

> "*Mr. Hobson, who was consul for the English at Venice having long been affected with stone in the kidney was at length attacked with a fit of such duration and violence that he was reduced to desperation. Finding no relief from any means that he had used, he addressed himself to Dominicus de Marchetti, a famed and experienced physician at Padua, imploring him to cut the stone from his kidney. He added that he was not insensible to the danger, but that death itself would be infinitely preferable to life and the misery under which he had long groaned. Marchetti seemed very desirous of declining not to operate, since the operation represented the extreme hazard, was impracticable and one he had never attempted, and that to proceed to it was in effect to destroy him* (i.e., Hobson). *But Mr. Hobson persisting, said that if he refused he would not desist until he had found someone who could do the operation. His resolution and importunity at length prevailed upon Marchetti to undertake the operation* [26].
>
> *Having prepared his patient as he thought convenient he began with his knife cutting gradually upon the region of the kidney affected, until blood disturbed and blinded his work he could not finish the operation at one attempt. Wherefore dressing up the wound till the next day he then repeated the operation and accomplished it by cutting into the body of the kidney and taking thence three or four stones. He dressed it up again. From this instant Mr. Hobson was freed from the severity of his pain and in a remarkably short time was able to walk about his chamber having been in no danger either from the flow of blood or fever. Marchetti continued to dress the wound for a considerable time, but he was not able to close it up. It soon became fistulous from the continued flow of urine through the sinus. Being in other respects restored to his former health and vigour and the matter discharged being little, Mr. Hobson took leave of the professor and returned to Venice under the care and management of his wife. One morning as she was dressing the wound she fancied she felt something hard and rugged as she wiped and, upon examining it a little more closely with her bodkin, which served her instead of a probe she found it to be a stone of the shape and size of a date stone, which being removed Hobson never afterwards complained of the least uneasiness in that part* [26].
>
> *About ten years later Hobson returned to London, where the Learned Dr. Tyson, and myself, were by Dr. Downes, who had known him formerly in Venice, invited to see him, which we did at the Castle-Tavern in Pater-Noster-Row; where, after we had received this Account from himself, he gave us the Satisfaction of viewing the Sore, which continued open, and permitted me without any Complaint (the Callosity being great) to pass my Probe so far into the Sinus, that we concluded it reached into the kidney: the Matter it then*

discharged was but little in quantity, but always diluted with and smelt strong of Urine. The Orifice would sometimes close for three or four Days together, and then the Matter made its way through the common Passages with the Urine, yet without any difficulty or Pain. There is no question, but there was a Coalition of the Kidney, and the Muscle Psoas. When we saw it he applied nothing to the Orifice but a clean linen Rag, which had a strong Urinous Scent. He was then as able in his appearance, to perform all the Functions of life, and to undergo any Fatigue, as any Man of his Years; being then, I conceive, upwards of Fifty, and was the next day to ride Post 40 or 50 Miles. I have heard that he is since dead, but could not be informed of what Disease" [26].

Samuel Pepys' Bladder Stone

It is a fitting conclusion to this particular chapter discussing famous and world record stones to close with the famous bladder stone of Samuel Pepys. It was large, to be sure, described to be the size of a tennis ball, but in 1658 this would be the size of a good hen's egg now (tennis balls have gotten larger it would seem). Samuel Pepys is not really remembered for anything significant except his diary which coincided with momentous times in London, England, and the world. In addition, Pepys had adapted a secretive writing style of shorthand called tachygraphy of Thomas Shelton and further secreted by adding French, Spanish, Latin, and Greek words. In other words, Pepys thought that no one could ever read his writings and he was genuinely honest in his documentation. The diary began on January 1, 1660, and continued for 9 years, until the death of his wife and the deterioration of his eyesight in May of 1669 [27]. During this time he had witnessed the Great London Plague of 1665, the Great London Fire in 1666, and the attack of the Dutch Fleet in 1667. He also was in a privileged position to observe and witness the response from the government [28].

Pepys' diary starts about one and a half years after his fateful encounter with perineal lithotomy. But he discussed it frequently and mentions the pride in his trophy, the bladder stone. Samuel Pepys came from a family of stone formers, like the Walpoles. His mother had stones and apparently passed hers and demonstrated the culprit to her fifth out of 11 children, Samuel. His maternal aunt and a brother also had bladder stones. Samuel began to have symptoms of the stone in his 20s while an undergraduate at Magdalene College with abdominal pains and gross hematuria. By the winter of 1657, the pain was becoming unbearable afflicting him daily. In his own words later, he commented that "*a condition of constant and dangerous and most painful sickness and low condition and poverty*" [27]. He consulted with Mr. Thomas Hollier who was the surgeon at St. Thomas and St. Bartholomew in London. It appears that Hollier's reputation was soaring because the previous year, 1657, he operated on 40 patients with all surviving. Samuel's father gathered the family together to pray for their son and brother and the surgical procedure was scheduled for March 26, 1658, at the home of his cousin's house, Jane Turner. There is no actually description of Pepys's surgery, but his friend John Evelyn recorded that his friend had removed a stone the size of a tennis ball. In addition, a prescription was given to Pepys which is part of the Hans Sloane Collection at the British Museum as follows [29]:

Rx Pulv. Glye. Rad.	ʒiii | Lactis vaccinæ	
Rad. Altheæ	ʒii | Aq. Roarum rub.	lb. iss
Fol. Malv.	M.* iiii | Alb. Ovorum No. xv.	
Cinnamomi fract.	ʒiss |	
Misee ante et distillantur lento igne.		
Sumate hujus ʒ vi; Syrup. Altheæ ʒ i½ omni mane et horâ somni quotidie.		
Mr. Peapes.	Dr. J. M.	

There was a note stating, "*For Mr. Peapes who was cut for ye stone by Mr. Hollyer, ye 28 March 1658 and had a very great stone taken that day for him*" [29]. The prescriber was James Moleynes who was also a surgeon but was senior enough that he could write prescriptions and sign with his initials. The chief constituent was lemon juice with syrup of radishes. They expected him to be feverish as this was commonly used for this problem. Pepys also was a curious fellow being a member of the Royal Society and eventually president of this organization. On February 2, 1662, 4 years following his lithotomy, he and some friends visited Chirurgeon's Hall. They listened to a lecture about the anatomy of the kidney, ureters, etc., and then went to watch an autopsy. He states, "*I did touch the body with my bare hand; it felt cold, but I thought it was a very unpleasant sight*" [29]. Pepys sometimes would take his stone in his overcoat pocket to show to friends. On March 26, 1660, he wrote, "*This day it is two years since it pleased God that I was cut for stone at Mrs. Turner's in Salisbury Court. And did resolve while I live to keep it a festival, as I did the last year at my house and for ever to have Mrs. Turner and her company with me*" [28]. In two more years he again noted the occasion, "*Up early, this being by God's blessing the fourth solemn day of my cutting for the stone. At noon came my good guests. I had a pretty dinner for them*, viz., *a brace of stewed carps, six roasted chickens and a jowl of salmon hot for the first course; a tansy and two neat's tongues and cheese the second, and were very merry all afternoon, talking and singing and piping upon the flageolette. We had a man cook to dress the dinner and sent for Jane* [Mrs. Turner] *to help us*" [28]. Pepys subsequently had a gilded display case constructed for his bladder stone that cost him 25 shillings.

Pepys had subsequent bouts of colic, probably ureteral, and had an autopsy after he died in 1703. He was treated for stone disease on July 1, 1664, by Dr. Burnett. He was given a mixture of "*Marsh Mallows, cumfry, liqourish, St. John's wort, leaves of plantan, alehoofe, red roses, cynament, and nutmeg*" [29]. John Shadwell, Hans Sloane, and the surgeon Charles Bernard were all present and recorded that his left kidney contained seven irregular stones with adjacent areas being quite inflamed. They also noted that the area of his bladder was thought to be gangrenous near the region of the lithotomy, and they mentioned it might have broken open again.

Conclusions

This chapter is unlike any of the previous chapters as it represents a compilation of unusual stone cases. These are the largest, most numerous, most nefarious, the smallest, or even those that led to the ultimate, in desperation, self-performed surgery. They represent a wide range of human sufferings from urolithiasis from the earliest days to the most recent. These are the stories that are needed to completely encapsulate the full history of urolithiasis. These historical records need someplace for compilation and comment. They belong to a comprehensive history. Mankind's morbid fascination with the unusual and famous is well known, which is why there continues to be such a fascination with world's records, such as who can eat the most hotdogs the fastest.

But urolithiasis is a non-self-imposed record that some would definitely not desire to become champion. No one voluntarily submits himself/herself to the agonies of stone recurrence except in those cases we've also looked at in the Fictitious Stones chapter. In the overall scheme of history, urolithiasis is perhaps insignificant compared to wars, famines, plagues, and even perhaps to World's Fairs and World's Series. The records of sports have its rabid fans who can quote statistics after statistics. There is no one who can do the same for urolithiasis. The stories themselves are buried and forgotten, but the people who lived and performed in the past, such heroic efforts in trying to allay the pains and sufferings of themselves and others deserve some notoriety. They should not be allowed to pass quietly into the night of historical pasts.

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28 Lithotripsy: From Rocket Science to the Clinic

Introduction

> "*Pain, hemorrhage, infection, the three great evils which had always embittered the practice of surgery and checked its progress, were in a moment, in a quarter of a century (1846–1873), robbed of their terrors*." [1]
>
> —William Stewart Halsted, June 27, 1904

In this the final section on the history of surgical methods of treating stones, we will focus upon the most modern methods of destroying calculi. Here we will explore methods though that do have some fascinating history in their own right and great future potential. The promise of energy-mediated stone destruction began early in the surgical evolution of stone disease, earlier than most current clinicians typically give credit to past investigators. In fact, some of the early investigators of electricity itself tried to devise ways to use this new energy to destroy bladder stones. The ability to comminute urinary calculi has always been regarded as technically demanding. Mechanical lithotrites were developed for nonvisual contact, tactile lithotripsy of bladder stones. The advent of optical imaging telescopic techniques made visual lithotrites the next great advance. Mechanical disintegration of stones has been limited to the lower urinary tract because of the relative large sizes necessary for these intricate devices to punch a calculus into smaller fragments [2]. Because of continued progress of endoscopic, minimally invasive methods to alleviate calculi, powered intracorporeal lithotripsy methods were developed.

Lithotripsy is the energetic method for trying to destroy urolithiasis in all parts of the urinary tract. In order to provide safely these energetic modalities, methods for safely delivering them in the urinary tract had to be developed. In the previous chapter on *Imaging the Beast*, we have discussed the history of both X-rays and endoscopic urologic surgery. We will not digress much into this history again; however we will spend some time on the approach to each area of the urinary tract. For instance, bladder stone lithotripsy has four methods that can be utilized: open surgical, transurethral which is considered to be a natural orifice type of procedure, percutaneous approach to the bladder which is suprapubic cystoscopy, and extracorporeal shock wave lithotripsy. The ureter can also be treated via the similar four approaches: open, percutaneous transrenal antegrade ureteroscopic, retrograde transurethral ureteroscopic, and extracorporeal shock wave lithotripsy. The kidney also has four approaches: open, percutaneous nephroscopic, retrograde ureteropyeloscopic, and extracorporeal shock wave lithotripsy [3]. Notice there is much overlap of the regional anatomical sites where stones can be attacked. All the modern modalities are now capable of being applied in any given scenario. The open methods have now almost become a method primarily dealt with in history books.

The remainder of this chapter will primarily focus upon the historical aspects that the methods

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of application of energetic methods have become developed and deployed for performing lithotripsy. We will try to conserve some order in these methods of lithotripsy. We will start with electrohydraulic lithotripsy because it was the earliest method conceived but had to await the engineering talents of the twentieth century. Next we'll present ultrasonic lithotripsy which began to be explored in the mid-nineteenth century. Explosive lithotripsy will follow with a discussion of ballistic lithotripsy. Laser lithotripsy and extracorporeal shock wave lithotripsy were the final developments towards the end of the twentieth century and space-aged engineering. Our discussion section will focus upon some future technologies that might yet develop into the future methods of treatment by lithotripsy.

Stone Destruction: Terms

What's in a name? [4]. The root *litho* comes from λιθος (lithos) and the various suffixes describe the methods of breakage or destruction. We've already come across lithotomy—to cut for the stone. The term lithotrity coined by Civiale implied breaking of the stone by crushing. We've encountered litholapaxy, coined by Bigelow, meaning to break up the stone (crush) and evacuate the fragments. Now technology will accomplish this same breaking up of stones, but the terms become more complex; we need Whewell. Comminution is the term engineers utilize to break down an object into pieces. This would apply to all of the modalities we will discuss here. Lithotripsy is any attempt to break down a stone using an energetic source. There have been many different types of energies utilized including the following: microexplosive, electrohydraulic, ultrasonic, vibrational, laser, and shock waves. The ultimate goal would be an energetic source that could be applied to destroy any and all types of stones, in any location, without injury to the urinary tract itself. We do not yet have such a device [5]. Each of the lithotripsy methods we will explore have advantages and disadvantages. Some of them have already been relegated to the past and are included here specifically because they are entirely historical, such as microexplosive and electrohydraulic lithotripsy. There is virtually no further literature that presents any therapeutic outcomes with these two modalities. Ballistic lithotripsy which involves a moving impactor is still occasionally being used in some places where more expensive and sophisticated lithotriptors are not available. Of course, any of these lithotriptors are capable of being combined for improved efficiency or to make a faster comminution of a calculus possible. In addition, some types of lithotripsy, such as ultrasonic and ballistic types, are capable of being used with suction aspiration to clear large volumes of stone debris. This insures that the patient does not have to pass the fragments and that fewer fragments are left behind that could serve as nidi for continued stone reformation.

What about the terms lithotriptor and lithotripter? Classically utilizing terminology derived from the rootstock of English, the "or" suffix implies a primary noun, whereas the suffix "er" would imply one who uses the proper noun or when used as an adjective, such as Tolley's Scottish Lithotripter Centre [6]. So a nuclear reactor is something that sustains a chain reaction of fissionable materials in order to create heat and ultimately electricity [7]. We will evaluate near the end of this textbook some of the reasons for selection by the physician (lithotripter) of which method of lithotripsy to apply in any given scenario (*Six Sigma*). In one large recent study, Childs and colleagues noted that surgeon factors significantly affected the lithotriptor modality. Shock wave lithotripsy was found to be associated with community urology practice, increasing time since training, shock wave lithotriptor ownership, and concern for stent pain. Ownership of a lithotriptor was associated with a 3–4-fold increase in the likelihood of choosing this modality over ureteroscopy or percutaneous nephrolithotomy [8].

Microexplosive Lithotripsy

The only current place where a student of the history of lithotripsy might come across microexplosive lithotripsy is in a historical account of lithotripsy itself. Knudsen and Denstedt did not even include this in their overview of intracorporeal lithotripsy in 2007 [9]. Microexplosives must be stored and secured in our modern age of terrorism and psychotic public attacks upon innocent victims, making this method too contentious to even be considered. But historically, it was tried and investigated and deserves some mention in a comprehensive history. Essentially all of the work was conducted in Japan throughout the 1980s. Wantabe first described a prototype apparatus for microexplosive cystolithotripsy in 1980 [10]. Here the authors utilized a model calculus in a pig bladder to implant and explode microcharges of explosives onto the implanted calculi. Fragments were then removed by aspiration. The method of delivery was a novel delivery catheter with 5 mg. of lead azide explosives. They noted that external charge blasting and confined blasting resulted in significant improvement of stone destruction with the latter method and that this was the method of choice for engineers who are destroying rocks industrially. They further noted that the detonation power of these catheter-based-directed microexplosives was 10–50 times larger than external explosives. These investigators followed the preliminary work with the first clinical application of this technique in 1983. They reported using their novel microexplosive catheter system in three clinical cases of bladder stones ranging from 32 to 65 mm and were successfully fragmented using 1–8 explosions. The fragments were all subsequently evacuated [11]. The group continued to accrue cases at Kyoto University and presented 105 consecutive cases with the average weight of bladder stone removed being 18 g (range 2–305 g.). There was one reported case of *minor extraperitoneal bladder perforation* which resolved spontaneously several days later [12]. Uchida last updated this series in 1989, now up to 130 cases. They no significant improvements however but concluded, "*We consider that any bladder stones*, *however big or however many*, *can be treated by microexplosion lithotripsy with confined blasting*" [13].

That would in theory be the end of this story; however, there is intriguing research in this field that has been ongoing. Microexplosive systems have now been developed that are even safer, more refined, and far more sophisticated and versatile than ever before. Some are fused with digital microsystems to perform all kinds of ingenious work, such as microwelding, tissue resurfacing, and many other applications. Such devices now typically have an initiator consisting of capacitance discharge unit (CDU) that fires 10-μm-thick wire (typically gold) or metallic film embedded in the detonable film [14]. In addition, the use of microexplosive to generate high-energy shock waves that could be applied extracorporeally has also been investigated [15]. These investigators created a silver-azide microexplosive underwater coupled device using 10-mg pellets fired in a semi-ellipsoidal reflector which one might expect to behave differently from a electrohydraulically produced shock wave. At this late stage in the history of urolithiasis, one might well suspect we have not seen the last of microexplosives despite their manifold risks and dangers.

Electrohydraulic Lithotripsy

Electricity was an eighteenth-century mystical wonder. Luigi Galvani was born on September 9, 1737, in Bologna and his father was a physician. He studied medicine and anatomy at the medical school in Bologna. In 1764 he married the daughter of his anatomy professor, and he became interested in experimental physiology. In 1766 he began to experiment with static electricity. He invented a metallic arc that made the muscles of a frog jump [16]. By 1783 he began to investigate electrical nerve conduction using the frog's sciatic nerve. He was a popular teacher and became the school's president in 1772. He published his monumental work, *De Viribus Electricitatis in Motu Musculari* in 1791 [17]. His work spawned a massive degree of interest by others all over the world. But Alessandro Volta was perhaps the most vigorous enthusiast who also became his most vocal detractor. But it was Volta who coined the term galvanism, but Galvani correctly interpreted that the stimulus was an electrical current. In 1790 Galvani's wife died and he was dismissed from the university because he refused to take the oath of allegiance to Napoleon who had occupied Bologna. He died 8 years later [18]. It did not take long for the new energy to generate interest in those studying stone disease. In 1803 G.A. Mongiardini and V. Lando tried to dissolve a calculus by galvanism without success [19]. The French chemists Prevost and Dumas followed this lead by developing a double sound communicating at one extremity with the bladder and at the other end connected separately with the poles of a voltaic pile. They thought that the acids and bases might be separated. They picked a fusible calculus (mixed struvite and carbonate apatite) treated with 120 pairs for 12 h, and each pile was recharged every hour. Platinum wires were placed at different points on the calculus in vitro immersed in water. A fine powder was noted arising from the stone which reduced from 92 grains down to 80 grains [20]. A second study reduced the stone to such a fragile state that it broke into small particles. They moved on to a dog model. A stone was placed on a sound that could be removed for study into the bladder of a dog. The bladder was irrigated with warm water and the current was applied for 1 h. The stone was analyzed and this was repeated morning and night for 1-h intervals for 6 days. They noticed that by the end the stone was so fragile it crumbled spontaneously. They removed the bladder for examination and noted no identifiable abnormalities from the electric current [20].

M. Bonnet from Lyons was the next to investigate the use of electric current on enhanced chemolysis of stones. He placed different types of calculi between platinum wires with dilute nitrate of potash. He noted that only the calcium of lime (calcium oxalate) stones resisted the action of the electric current, while all other stone types rapidly dissolved [21]. During these experiments, Bonnet also changed the salt solutions trying the phosphate, the muriate, and the borate of soda; he tried the fumate of potash, but none of them generated the action that the nitrate salt for dissolution. Later that year, Henry Bence Jones confirmed these findings and demonstrated that the current did dissolve calcium oxalate stones as well, but the process just took longer [22]. Dr. Melicher of Vienna reported using a voltaic pile of 100 plates to dissolve calculi in vitro in 1848 [23]. He also developed an innovative stone grasping electrode unit to grasp the stone and clinically tried this in two patients in which parts of the stone were dissolved [23]. This was the heady environment of research on electricity that a young German academic found himself in 1813. Franz von Paula Gruithuisen (1774–1852) published his paper *Should One Abandon the Long-standing Hope of Being Able to Remove Bladder Calculi Mechanically or Chemically Sometime in the Future*? in the 1813 Journal of Medicine and Surgery [24]. Gruithuisen began his experimental researches in 1809 and the concept of using a galvanic current to produce a spark in order to break the stone into pieces [25]. The electric current was delivered to the stone by two platinum wires via his metal tube but insulated by glass. His source of power was a voltaic pile of platinum discs separated by silk and covered with "*gum lac*" [26].

George Robinson followed this with his attempts to pulverize phosphatic, mulberry (calcium oxalate), and lithic acid (uric acid) stones with electrical sparks. He developed an innovative elastic catheter with two conducting wires separated by an inner and outer coating of the jar [27]. He proceeded to break uric acid stones in vitro and stated, "*it not unfrequently happened that the glass or earthenware was fractured as well as the stone*" [28]. One response in The Lancet stated, "*Leaving out of the question altogether the propriety of executing very powerful electrical discharges in the human viscus, and the possibility, not to say probability, which exists of the extreme danger of such a practice, we hold, as a result of an intimate acquaintance with the use of instruments in the organ, that it would be by no means an easy thing to maintain the mere point of any catheter accurately against the side of a stone, in order to conduct the discharge; and then subsequently against every fragment of it, until a sufficient amount of disintegration had been performed*" [29]. The pessimism aside, the comments were based upon blind attempts to deliver this force on the stones. Dr. Robinson for his part concludes with the following comment, "*On the whole, I am of opinion that the electrical force applied in the manner indicated, will be found quite as efficient for the disintegration of calculi in the bladder as the more formidable analogous operation of lithotrity, occasionally practiced. And, as regards simplicity and security, the electrical apparatus certainly appears preferable to the instruments used for crushing the stone by ordinary mechanical force*" [29]. It would take another 100 years to develop Dr. Robinson's idea. Robinson in his book noted that he got many of his ideas on breaking stones from Andrew Crosse's experiments on fracturing glass with electrical currents [30].

Reinhold Wappler reported on the abilities of electrical "sparks" to destroy both hard and soft calculi in his 1913 catalogue, possibly recalling Robinson's work. Lew Alexandrovitch Yutkin, a Leningrad engineer, patented and constructed an impulse generator and the probe for endoscopic bladder stone destruction. Dr. Victor Goldberg fragmented the first human bladder stone on July 5, 1959, and reportedly fragmented a ureteral calculus on December 9, 1959, using this device, the Urat I [31]. Büttger described the first series with this device [32]. Kumanov followed with a series from Bulgaria, Olaf Alfthan from Finland, Rouvalis from England, and Albrecht from Germany [33–36]. Michael Tidd reported on the physics of the new EHL devices [37]. He begins with cautionary concerns that we encountered from the work of Robinson almost a century earlier: "*Your interesting leading article suggests that electronic stone disintegration is a safe method of dealing with vesical calculi, though not without significant disadvantages. In my view the method is also accompanied by distinct hazards*" [37]. He then proceeds to discuss the physics of the device: "*Each underwater spark produces not only the shockwave which you mention but also a bubble of vapour, which expands and contracts extremely rapidly in oscillatory fashion in the subsequent five or so milliseconds. The maximum size of this bubble depends among other things on the electrical energy used, but in one instrument an energy of 18 joules produces a bubble approximately 3 cm in diameter. Each time the oscillating bubble reaches a minimum volume it emits a pressure pulse and the first one or two pulses are comparable in destructive force to the preceding shockwave. The process has many similarities, except in scale, to the underwater detonation of high explosive*" [37]. He is concerned about the power settings and the unintended risks of bladder perforation, even the possible energetic projectiles created from ejected stone fragments. He expressly is concerned about this ability in the small confines of the ureter.

Complications were reported early such as the device failing to break up large, very dense stones, instrument breakage, and prolonged operative times [38]. Electrohydraulic lithotripsy represents an unfocused energy modality that is potentially dangerous if used in an uncontrolled fashion. Nonvisualized balloon-protected delivery devices have been described to place small electrohydraulic probes in direct contact with concretions with some degree of success [39]. Despite multiple series documenting its clinical efficacy, many investigators are concerned about the relatively uncontrolled energetic source from the electrohydraulic probes. Smaller sizes and solid-state electrical conduction apparatuses have further diminished the potential injuries and increased the clinical efficacy of this method of direct contact lithotripsy [40].

A recent excellent prospective evaluation of electrohydraulic lithotriptors was reported by Burn's group in Alabama. All available EHL devices did perform well in the in vitro portion of this study. There was no reproducibility of the power from probe to probe with any of the manufacturer's products. Variability of decay of the efficacy of these probes was evident in all of the manufacturer's devices. Some stone types did better with the Circon/ACMI EHL unit whereas the others did better with the Storz unit. All in all, electrohydraulic probes were unpredictable and the power settings recommended by the manufacturers did not parallel clinical experience with these devices. Decay and the need to utilize several probes per stone were fundamental to all of the manufactured units. The death knell of electrohydraulic lithotripsy, however, did not come from its own shortcomings; plentiful as they were, it came from lasers [41].

Ultrasonic Lithotripsy

The use of ultrasound to destroy urinary and biliary calculi is not new, and the foundations begin in the technologic outpouring of engineered devices following World War II. The principles of devices currently utilized today were elaborately outlined in full in an article by Harold Lamport and Herbert F. Newman in 1955 [42]. Mulvaney in 1952 attempted to destroy stones using a 0.8-kHz device [43]. Coates achieved partial stone fragmentation using a 15-kHz device in 1955 [44]. Both of these studies utilized high-frequency ultrasound to overcome the structural adhesive properties of urinary calculi. Both failed, but the concept remained intriguing and has been reinvestigated throughout the ensuing decades. Zheng and Denstedt describe four methods of generating ultrasound waves, mechanically, thermally, electrostatically, and piezoelectrically, but Lamport and Newman had already presented the strengths and weaknesses of each of these [45]. All current handheld sonotrodes utilize the piezoelectric method of generating the ultrasound waves. By the early 1970s ultrasound energy in the 20–27-kHz range was transduced into mechanical energy producing longitudinal and transverse vibrations that could effectively comminute calculi [46–48].

These authors performed the principle investigations of this intracorporeal lithotriptor and elucidated the fundamental aspects for successful lithotripsy. The probes need to maintain contact with the targeted calculus under direct vision. In addition, by removing stone debris continuously via suction, the comminution would facilitate continuous contact. Throughout the remainder of the 1970s to the early 1980s, these ultrasonic lithotrites became commercially available for use upon vesical calculi. Terhorst fragmented a bladder stone in vivo in 1972 [46]. In 1979, Marberger, Alken, and colleagues utilized a 23–26-kHz ultrasonic probe for intracorporeal lithotripsy [49, 50]. In 1977, Kurth and Rathert used these instruments to comminute renal calculi via antecedently placed nephrostomy tracts [51]. The fundamental principles of the ultrasonic lithotrite next need to be addressed. The concept of intracorporeal lithotripsy has as its foundation, the minimally invasive notion that by avoiding an open operative intervention, the patient obtains a significant therapeutic benefit. By introducing a powered apparatus, such as an ultrasonic lithotrite, the ability to comminute a large calculus into smaller more easily extractable pieces is possible [3].

The currently available ultrasonic lithotripsy units consist of several separate but noninterchangeable pieces. The first is the ultrasonic generator that houses the electronics that power the transducer. This electrical generator is powered at about 100 W. The electrical energy is transduced into high-frequency, ultrasonic sinusoidal oscillations via a separate transducer. All of the available units have the transducer in an attachable handpiece. The handpieces are complex mechanical devices consisting of two acoustical end parts, separated by piezoceramic elements (Fig. 28.1). It is the piezoceramic elements that are powered by the generator to produce high-frequency sinusoidal vibrations of 20–27 kHz. The acoustical resonators then determine the impedance, and a long, hollow steel probe transforms the ultrasound energy into transverse and longitudinal vibrations. Direct contact with the probe's tip is necessary to transmit the vibratory energy to the calculus. The lengths of the hollow probes are fixed by acoustical parameters that can affect their performance. It is the ratio of the lengths of the acoustical end parts that predict the wavelength of the vibrations. Both the size and shape of the acoustical horn transforms the amplitude of the vibrations. The longitudinal vibrations of the probe are responsible for the efficacy of comminution. It has been ascribed that as the probe's tip contacts the calculus' surface, the contact plane mechanically shatters the crystal lattice producing cracks in the stone's surface and small particulates becoming dispersed. One investigation states that the amount of matrix proteins absorb the ultrasonic vibrations and produce the microfractures that result in comminution [52]. There is no basic scientific evidence to support or refute this theory. The hollow bore is essential on large-volume stones to maintain

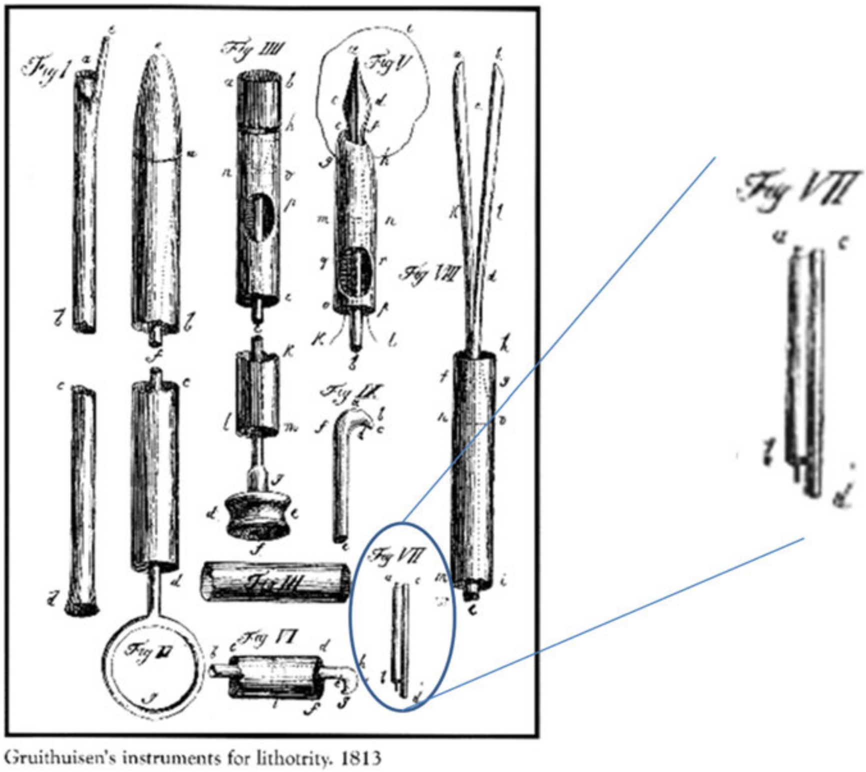

Fig. 28.1 Franz von Paula Gruithuisen's 1813 illustrations of his transurethral lithotrity instrumentation. (*Fig. I*) Perfusion system. (*Fig. II*) Component of lithotrepan. (*Fig. III*) Length was 45 cm. (*Fig. IV*) Housing of lithotrepan. (*Fig. V*) Wire loop catches and holds stone. (*Fig. VI*) Hook for crushing stones. (*Fig. VII*) *Galvanic spark device*. (*Fig. VIII*) Two-armed crushing forceps

contact (aided by suction), provide cooling of the handpiece (continuous fluid aspiration), and clear the dispersed particulates thus improving optical visibility.

All types of common human uroliths have been successfully treated in vivo with ultrasonic lithotrites. The success rate has been reported to be as high as 69–97 % [45]. Exceptions though infrequent are possible and the prudent endourologist should be highly aware of "*non-fragmentable*" calculi [53]. In looking closer at the comminution process utilizing the ultrasonic lithotrite, the following have been identified as variables that alter efficiency: chemical composition, size and density of the calculus, surface features of a stone (smooth vs. irregular outer surface), and length of time the stone has been present. The efficiency of the probe increases with better contact with the stone. There is evidence that the larger the probe's bore size, the more efficient the comminution. In addition, the larger bore allows pieces of larger size to be aspirated. It is also known that the amount of pressure applied to maintain contact with a given calculus affects the efficiency of comminution. That is to say that by lightly touching a stone's surface, less transmission of vibratory energy occurs and smaller pieces can be obtained. For every stone type and configuration therefore, the intracorporeal lithotripsy utilizing a hollow-probe ultrasonic lithotrite must be continuously appraised. There are no current well-documented studies utilizing this power source that demonstrate that a certain "technique" utilizing an ultrasonotrode is superior to another. There exist principally two opposing although not mutually exclusive philosophies. The first is to rapidly comminute a concretion by firmly deploying the sonotrode

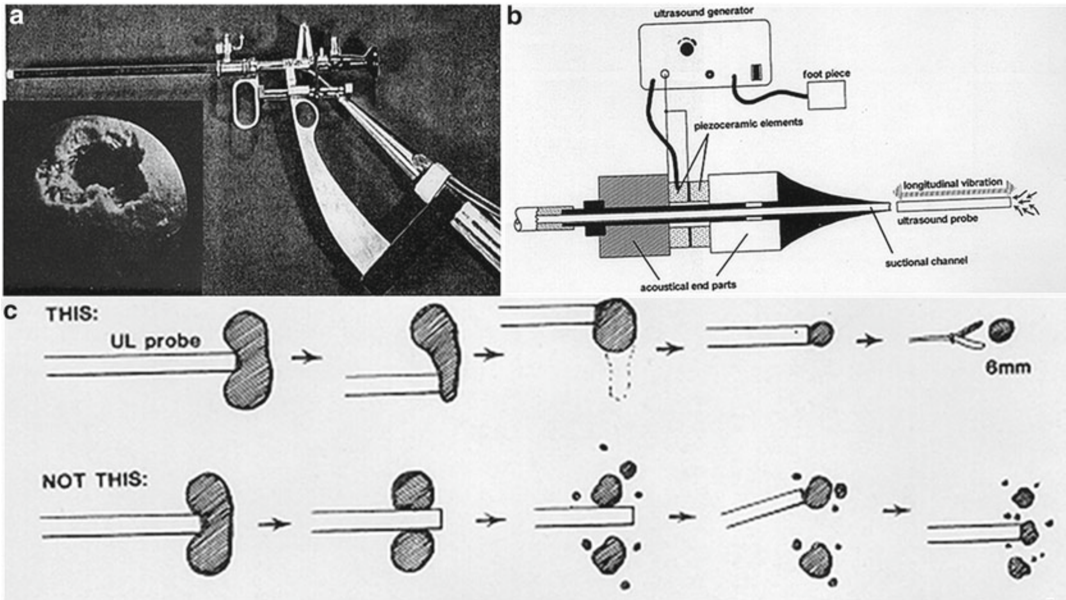

Fig. 28.2 (**a**) The prototype ultrasonic lithotriptor from Terhorst, Lutzeyer, Cichos, and Pohlman [19]. (**b**) The current handpiece containing the piezoelectric transducer for intracorporeal ultrasonic lithotripsy [4]. (**c**) Technique described by Clayman in *Techniques in Endourology* for intracorporeal ultrasonic lithotripsy [27]

upon the stone's surface. Large cracks and fragments will be produced. The larger pieces can then be extracted piecemeal with graspers or the Wickham triradiate extractors [54]. The second method utilized during ultrasonic nephrostolithotripsy is a slower more delicate, lighter contact to aspirate and remove with the suction apparatus as much of the stone as possible. Since different stones respond variably, many times both methods are necessary. Clayman has best described the method of intracorporeal lithotripsy in his textbook *Techniques in Endourology* [55]. The goal is to perform the lithotripsy as soon as possible, leaving minimal to no fragments to insure a "*stone-free*" status at the conclusion. Given the understanding of the physical workings of the sonotrode, disintegration is best started at the surface periphery. In large stones, this is sometimes not possible, and a drill hole in the center of the stone's surface is best. Once an area of the surface has fragmented, the application should proceed best around the periphery; this methodical circumferential approach reduces the stone's mass in a fashion less likely to result in chasing chunk of material through the collecting system (Fig. 28.2) [55]. Small fragments that do break free must be taken care of as quickly as possible either by the lithotriptor or with forceps extraction (for pieces smaller than 8 mm). There will be no disintegration of the calculus unless the sonotrodes' tip is in contact with the stone's surface. Fragments of the stone are continuously evacuated from the inner aspect of the sonotrode during the lithotripsy. Smaller stones can be effectively removed in 5–15 min; larger stones can take up to 30–60 min [55]. This speed and efficiency is affected by chemical composition with some calcium oxalate monohydrate and some smooth uric acid stones having been reported to be refractory to ultrasonic lithotripsy.

Two other methods of intracorporeal ultrasonic lithotripsy are worth discussing, mainly for completeness and historical interest. The first is solid probe ureteroscopic ultrasonic lithotripsy. Prior to the advent of pulsed dye lasers and the holmium:YAG laser, the 2.5-mm. solid wire sonotrode from Karl Storz was an integral part of the endourologic armamentarium. For ureteral calculi, this solid wire probe was quite successful (87–98 %) [56]. The primary concerns were the inability to aspirate and the buildup of heat by the ultrasonic vibration. Larger rigid ureteroscopes were also required (9–13 Fr). The solid wire sonotrode was also deleterious to the optics of these scopes with deterioration of image quality noted with time and utilization. Another method investigated utilized a flexible solid wire sonotrode that could be utilized for flexible ureteroscopy. The special flexible ureteroscope was 13.2 Fr, quite large by modern standards. The flexible ultrasonic transmitter consisted of a stainless steel wire (0.5-mm diameter) encased in a 1.5-mm polytetrafluoroethylene (Teflon) tube. Water was required to cool the device during applications. A total of 16 patients were treated, and 18 stones were targeted in the initial trial of this device. There were no reported complications from application of the flexible ultrasonic lithotriptor, but there were two ureteral perforations secondary to insertion of the large ureteroscope. In addition, the flexible sonotrode reduced deflectability of the flexible ureteroscope to 30° and limited the ability to irrigate properly to enhance vision. The flexible ultrasonic lithotripsy failed in two patients due to technical problems from impacted stones [57].

Since its initial utilization in the mid-1970s and subsequent to the first published report by Kurth, remarkably few tissue-related injuries have been reported from ultrasonic lithotripsy [51]. In vitro work has demonstrated that the vibratory action of the sonotrode's tip produces very little damage to soft tissues. Probably related to the inherent elasticity of the uroepithelium and linings of the urinary tract, the sonotrode's vibratory energy causes only mild inflammatory response. When ultrasonic lithotrites were activated on rabbit bladder walls, lesions transmurally or even within the muscularis were not seen. No perforations were noted with continuous exposures up to 5 min at amplitudes below 20 μm. Edema and erythema were noted in the epithelial lining, but could not be distinguished from the same lesions caused by suction alone [58]. Frequency changes have likewise been noted to have minimal, if any, effect upon tissues. The vibratory effects and transduction of the ultrasonic energy do result in heat buildup. This potential for thermal injury can be minimized by continuous saline irrigation. At irrigation rates of 30 ml/min., the temperature increase at the tip of the sonotrode has been measured to rise only 1.4 °C [59, 60]. Terhorst and colleagues did demonstrate that the addition of the burr head to the sonotrode did result in the decrease of local heat generation over time. At 10 s of continuous ultrasound generation, the difference was 10 °C, by 30 s this difference rose to 14 °C, and at 60 s there was a measurable 21 °C difference favoring the burr-headed ultrasound probe [46, 61]. An additional safety feature on all ultrasonic lithotrites is the use by manufacturers of a thermally insulated jacket covering the housing of the handle of the transducer. This safety feature prevents inadvertent burns to the surgeon's hand during ultrasonic lithotripsy. In addition, if anyone has used the earlier sonotrodes, the newer units have also decreased in weight by over 50 % making them much easier to hold for a prolonged period of time. The manufacturers have also added noise-dampening features to the modern generators and transducers effectively reducing the noise decibel levels considerably [60]. The ultrasonic noise having the potential for auditory compromise of the urologist over time. Teigland and colleagues noted that in vitro noise levels were never greater than 103 dBA. During clinical cases, the actual noise levels were even slightly less, never greater than 100 dBA. In addition, they reported on the auditory testing of the senior investigator revealing preservation of hearing sensitivity [62].

The major real risk therefore of the ultrasonic lithotrite is the potential for the steel probe to produce iatrogenic injury by inadvertent penetrations through the epithelium or rough handling within the confines of the urinary tract. By passing this metal device beyond the targeted stone, the tip can be outside of the view of the surgeon. This potentially can result in inadvertent perforation of the collecting system. Clinical data is available on the long-term sequelae of intracorporeal ultrasonic lithotripsy [63]. Remarkably few instances of the sonotrode resulting in inadvertent injury are noted. In one of the largest long-term single institution series, Marberger et al. noted that in 82 patients followed for a mean of 22 months, residual calculi (9/82) and stone recurrence (2/82) represented the most significant risk [64]. Technical complications have been reported utilizing the small burr tip, hollow sonotrode from Karl Storz. Two cases of disruption of the tip requiring open ureterotomy for retrieval have been reported [65]. In addition, one more serious complication is noted to have lethal consequences during percutaneous nephrostolithotripsy. A lethal air embolism has been reported to occur when the roller pump irrigation system was connected backwards. Upon activation, instead of instilling the irrigant solution, air was pumped into the nephroscope and into the patient [66]. There have been no substantive reports of water intoxication or hyponatremic disasters probably owing to the fact that the electrolyte irrigation solutions do not hamper the clinical effectiveness of the ultrasonotrode and saline should be used automatically.

Outcome data for percutaneous nephrostolithotripsy was summarized by the AUA Nephrolithiasis Clinical Guidelines Panel in 1990 [67]. This included a meta-analysis of outcome data from 110 articles. Median stone-free rates for staghorn struvite calculi using percutaneous methods were 0.733 (95 % confidence interval 0.547–0.874). This was compared to ESWL with a median stone-free rate of 0.500. The median complication rate, including hydronephrosis, pneumonia, perirenal hematoma, vascular injury, urinoma, secondary unplanned interventions, and loss of kidney rates, was 0.074 (95 % CI 0.003–0.322). Median transfusion rate was 0.108 (95 % CI 0.003–0.478). Median death rate was 0.001 (95 % CI 0.0001–0.005). The number of primary procedures per patient was 1.486, and secondary procedures were required in 4.7 % of the patients. Long-term complications included stone recurrence (median 0.068 [95 % CI 0.015–0.176]), stone growth (0.070 [95 % CI 0.026–0.142]), and loss of kidney (0.016 [0.001–0.061]) [67]. In a retrospective analysis of patients undergoing ESWL or PCNL for upper tract stones, Deem concluded that PNL had a significant advantage of stone-free status versus shock wave lithotripsy for moderate-sized kidney stones [68].

Laser Lithotripsy

The next energetic modalities utilized to perform direct contact intracorporeal lithotripsy are laser sources. *Laser* (light amplification by the stimulated emission of radiation) is the acronym for the process of generating intense light energy. This was predicted in 1905 in a paper by Albert Einstein that light delivers its energy in chunks or discrete quantum particles which are now called photons (photoelectric effect). He followed this with his 1917 theory that, besides absorbing and emitting light spontaneously, electrons could be stimulated to emit light of a particular wavelength [69]. This theory foreshadowed the quantum physics that would eventually become focused upon quantum electronics in the 1950s. Gordon Gould in 1957 in a creative burst of intellectual energy came up with the idea of light wavelengths generated inside a gas-filled chamber with two mirrors that would amplify the beam and make in monochromatic. His notebook and patents were eventually used to prove that he indeed discovered the principle of lasers but the Nobel Prize went to others [70]. Laser technology rapidly took off in the 1960s and 1970s with solid-state lasers replacing gas lasers. Lasers are typically named after the substance that is used (or doped) to make a certain wavelength of light. CO_2 lasers would utilize the gas (or rarely liquid) as the lasing medium. A rod of crystalline material such as yttrium:aluminum:garnet (YAG) is utilized in many solid-state lasers with the addition of another material, typically a rare earth element to get a selected wavelength of emission. The most impressive technology of lasers is called a free-electron laser; this is capable of being tuned to a wide variety of wavelengths (from microwaves, visible spectrum, ultraviolet, and even X-rays) to experiment on lasing effects [71]. The power of a laser is different than other energy sources since the energetic beam is light itself. The wavelength of light, the pulse duration, the beam size, and the power (usually in joules) all have effects upon the targeted stone.

The first reported potential for the utilization of laser energy for stones was by Mulvaney and

Beck in 1968 [72]. It took some time from theory to application however; technical details such as heat generation had first to be controlled [73]. A stress wave of 34 kbar was generated in experiments. Stone experiments followed directly [74]. Fair utilized both a high-intensity pulsed ruby laser (Q-switched) and Nd:glass (Nd = neodymium, a rare earth element) laser to induce shock waves of up to 10 kbar that fragmented stones in vitro. A nominal 2-J laser was utilized to fragment different sizes; shapes, color, hardness, and composition were evaluated. Watson and colleagues utilized a Nd:YAG laser in 1983 to experiment on delivery of this energy via small quartz fibers [75]. In 1987 Graham Watson utilized a flashlamp-pumped tunable dye laser (coumarin green at 504 nm wavelength) to study the variables of wavelength, pulse duration, and fiber diameter to develop a usable system for clinical urology in pig ureters [76]. Perhaps the most important of several significant findings was that utilizing a laser, very little injury was noted in the tissues of the ureter. In fact, most of the trauma came from the introduction of the ureteroscopes (at this time they were quite large) [76]. This represented the fundamental impetus for the development of smaller ureteroscopes which rapidly evolved [77]. The tunable dye lasers never really achieved the degree of clinical success that might have been expected. Success ranged from 64 to 100 % with primary problems secondary to fragments and the size of the ureteroscopes at this time usually mandating the use of ureteral stents.

There are at least three mechanisms for stone disintegration from different laser types [72]. It is believed that continuous-wave lasers induce thermal stress fractures within the stone, resulting in their breakup, whereas flashlamp-pulsed lasers act by breakdown of the surrounding fluid into plasma, thereby creating a pressure shock wave resulting in subsequent stone comminution. The holmium:YAG laser may in fact have two primary effects that result in intracorporeal lithotripsy. First is this infrared wavelength is strongly absorbed by water with the development of a gas plasma as already mentioned. But there is strong evidence that the stone itself probably interacts with the wavelength and there may be actual loss of calculus material by thermal effects [73]. Clinically the holmium:YAG (Ho:YAG) has become the intracorporeal lithotriptor of choice.

As laser technology advances and newer modalities such as the Q-switched Nd:YAG, alexandrite, and excimer laser technology expands, more information on the clinical efficacy for laser lithotripsy will be available. The major factor prohibiting the generalized use of laser technology at present is cost. Current trends in laser lithotripsy research includes attempts to find safe laser wavelengths that would allow non-visualized, contact lithotripsy. The Ho:YAG laser clearly has major advantages over all other laser types at present [74]. Claims that this lone wavelength in the mid-infrared (2100 nm.) range both is capable of comminuting all stone types and is likewise capable of soft tissue ablations are beginning to be published with increasing frequency [75–77]. The holmium:YAG laser has evolved into the workhorse lithotriptor in places that have ready access to this technology. There is no stone type that is resistant to the powerful photothermal destructive mechanism of this laser energy. The fibers that deliver the laser energy are typically high-quality, reusable small fibers that can be passed under direct vision by a wide variety of both flexible and rigid endoscopes. There is virtually no region within the lower or upper urinary tract that cannot be accessed with a flexible ureteropyeloscope and targeted stones destroyed. Because of the ability of this laser to destroy soft tissues, the lithotripsy must be done in a carefully controlled manner with good visualization. The Ho:YAG laser is so good that it has given all other lithotripsy modalities significant competition and in some instances has replaced all of the alternatives.

Shock Wave Lithotripsy

"Not in the past 100 years has such an upheaval in medicine occurred: The "discipline of surgery" is joining the technological revolution and advancing the state of the art with laparoscopic surgery. This represents a radical shift in the concept of surgical practice. The "great leap of faith" has occurred; for the first time in history, surgeons are

performing surgical procedures without physically seeing or touching the organs they are removing or repairing."

—Satava, 1993

The next evolutionary modality would be a high-energy modality that could be beamed into the patient, like something out of Star Trek. This is exactly what has transpired. Shock wave lithotripsy utilized a high-energy wave that is generated outside of the body and focused upon the stone. So, it is by definition extracorporeal (outside of the body) and is beamed intracorporeally (inside of the body). The shock wave is a high-energy wave that can propagate through the body because the body is largely water as well. The history of shock wave lithotripsy is a modern history which has been so well documented that repeating it here would seem superfluous, since those that were principally responsible for its discovery, development, utilization, and application are still very much alive. In fact, the history of shock wave lithotripsy is best gotten from Dr. Christian Chaussy himself (recorded with sound) at http://www.webcasts.prous.com/cuaua2008 in his talk at the 4th International Symposium on the History of Urology, November 7–9, 2008, at the William P. Didusch Center for the History of Urology [78].

The NASA scientists became interested in the pitting problem of the reentry shields on the Mercury and Gemini spacecraft and knew that shock waves were responsible for the high-velocity reentry damage. A German aircraft manufacturer, Dornier Systems in Friedrichshafen (West Germany then), began to experiment with high-energy shock waves as well by 1963. They performed some experiments on human tissues in 1966. By 1974, a grant from the German federal government began experiments with the Institute for Surgical Research (Prof. W. Brendel) of the Ludwig Maximilians University in Munich. Professor A. Schmidt became involved in early experiments in cooperation with Dornier [79]. They recruited a young faculty member, Christian Chaussy, for extensive animal experimentation. This culminated in the first human being treated in a bathtub-like device on February 7, 1980, in Munich. The device was called the Dornier Human Model 1 (or HM1) [80]. All throughout 1983 patients were treated at the experimental unit in Munich, while modifications to the lithotriptor itself were being carried out at Dornier. In October of 1983 a second lithotriptor was installed at the Katharinen Hospital in Stuttgart under the direction of Dr. F. Eisenberger called the Human Model 3, or HM3. By March of 1984 the first unit was placed at the Methodist Hospital in Indianapolis, Indiana, with Drs. James Lingeman and Daniel M. Newman. The Dornier HM3 utilized a large, degassed water bath for patient submersion to couple the high-energy shock wave to the skin (entrance site). Biplanar fluoroscopy was used for guidance and monitoring lithotripsy. A semi-ellipsoidal reflector held a spark plug that was connected to an 80-nF generator. The shock wave lithotriptor has since undergone many generations of change and design, but the early results were impressive and have not been bettered by modern alterations. Yet, there have been adverse outcomes, with injury to the renal parenchyma itself being the most worrisome.

The noninvasive desire to break apart stones, kidney, ureteral, bladder, biliary, and salivary, has remained a lofty goal for such devices. They have spawned interest in treating other calcified soft tissues and even malignancies. The hope that this type of therapy would be the panacea for stone treatment has sadly not been achieved. Ongoing research in the basic science of the shock wave itself continues, and the hopes of discovering some methods of improving outcomes while decreasing the bioeffects upon the renal tissue continue. Wouldn't it be surprising that the generation of a shock wave by a microexplosive might be a better type of high-energy wave for comminution and solve the dilemma of destruction without tissue injury?

Discussion

"*The* ***macula levis notae*** *clung to surgeons the world over until the beginning of the nineteenth century, although distinguished and scholarly men, as well as charlatans and barbers, have practiced the art in almost unbroken succession from the time of Hippocrates (460–375 BC) to the present day.*

> *A warning for all time against satisfaction with the present achievement and blindness to the possibilities of future development is the imperishable prophesy of the famous French surgeon, Baron Boyer, who over a hundred years ago declared that surgery had then reached almost, if not actually, the highest degree of perfection of which it was capable*." [1]
>
> —Halsted

We have completed our history of the surgical alternatives for stone disease with this chapter on lithotripsy. Energetic modalities of every conceivable type have been tried to treat urolithiasis. Some have worked better than others, but the allure of a noninvasive technology has led to the development of high-energy shock wave lithotriptors. The history of lithotripsy parallels the development of the technology behind the powered source. Electrohydraulic technology followed the development of electrical apparatuses that really exploded in the Industrial Revolution. It is somewhat amazing that the work of Robinson was not taken up by others since endoscopic urologic evaluation was on the rise in the early twentieth century. Ultrasonic lithotripsy had to await the mastery of the generators as well as the transducers and much of this was invented during World War II for use in radar and sonar. Lasers of course were a newer invention, not without its convolutions. Finally high-energy shock waves were developed in the late 1960s through the 1970s before being applied to human stone disease. Stone disease need not be the nightmare so clearly represented in the historical past which we've spent so much time covering.

Early in the history of extracorporeal shock wave lithotripsy, the Health and Public Policy Committee of the American College of Physicians issued a statement entitled simply, "*Lithotripsy*" [81]. They were obviously proponents of the new technology noting specifically the high success rates in carefully chosen patients and low retreatment rates. This was a view of the new technology through rose-colored glasses. There is no question that shock wave lithotripsy revolutionized the therapeutic options for patients, but long-term potential sequelae would be unmasked such as risk for hypertension, diabetes, progressive long-term renal dysfunction, and the possible change from one stone type such as calcium oxalate to another more complex stone condition, brushite. There is much current basic science being done to advance the technologies of lithotripsy. For instance, one study from Banaras Hindu University investigated the use of artificial neural networks (ANN) to predict the optimum lithotripsy modality for a given patient's presenting scenario [82]. In this work they eliminate human subjectivity bias by stratifying preoperative data using a feed-forward, back propagation ANN with 37 variables. These included such things as clinical data, laboratory values, urinary findings, X-ray findings, and shock wave lithotripsy settings. This ANN correctly predicted the optimum fragmentation in 17/22 patients. In addition the ANN also correctly identified all 5 patients whom optimum fragmentation did not occur.

Perhaps the future of lithotripsy might come from the basic science of stones themselves. For instance, stones as well as most solid structures appear to have a measurable harmonic frequency that if stimulated will shatter the structure of that structure, like a wine glass with an opera singer. Little work on this has yet to identify a viable application of this theory to stone disease because of many variables involved and the physics is very elaborate and difficult [83]. In addition, it is quite possible that the holmium:YAG laser might not be the best for intracorporeal lithotripsy as well; research on another mid-infrared rare earth laser, the erbium:YAG (wavelength of 2900 nm), shows many advantages, but technical difficulties exist for manufacturing usable fiber guides [84]. Perhaps the free-electron laser will become the future device for deriving new therapies. There are now centers with such devices spreading around the globe and medical applications seem to invite applications. Lasers that can now fire in the femtosecond range (10^{-15} s or a quadrillionth of a second) are being evaluated for possible use as lithotriptors [85]. In 1951 Paul L. Singer described a device that he believed would revolutionize urologic management of ureteral calculi—the nylon thread ureteral stone extractor [86]. We have come a long way, but the future is bright for energy sources solving the final problems for lithotripsy—stone destruction or comminution with no tissue injury.

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29 Modern Stone Science

Introduction

> "*That man can interrogate as well as observe nature was a lesson slowly learned in his evolution. Of the two methods by which he can do this, the mathematical and the experimental, both have been equally fruitful- by the one he has gauged the starry heights and harnessed the cosmic forces to his will; by the other he has solved many of the problems of life and lightened many of the burdens of humanity.*" [1]
>
> —William Osler, The Evolution of the Idea of Experiment in Medicine, 1907

It is now time to turn to the development of our current "state-of-the-art" knowledge of stone disease. This is largely a tale of late twentieth-century and early twenty-first-century science. We will discuss the theory of modern stone formation that had its origins with Alexander Randall's fortuitous identification of his eponymous plaques on the renal papillae of cadavers and how this model has evolved into a modern synthesis trying to explain all the common denominators of stone formation. This is a collaborative tale, involving groups of clinicians and scientists who would meet from time to time and compare notes, facts, trends, and speculations. By 2004 the globalization of urolithiasis interest culminated in the development of the International Urolithiasis Society. Their Preamble states "*Urolithiasis is condition affecting most societies on Earth. An International Urolithiasis Society (IUS) was formed to facilitate advancement of the scientific knowledge, medical investigation, and treatment of urinary stone disease throughout the world in the interests of the peoples of the world*" [2].

Having introduced the collaborative method of shared information, the meetings themselves are difficult to present historically. First, it is impossible for anyone to distill the essence of a complex meeting into a few summarization sentences. Second, the conversations and verbal portions are often where the true advances or eureka moments have occurred, making their recorded histories impossible to unearth. But they often do leave lasting legacies, such as printed Proceedings of the meetings, and these are generally available for inspection. They lose much of the flavor of the meetings themselves but accurately record the science that was presented. Bichler from Tübingen, Germany, undertook the monumental effort to review the European collaborative urolithiasis meetings in 2006 [3]: "*Of decisive importance for the many research groups all over Europe were the scientific symposia dealing with the theoretical foundations and clinical aspects of urinary stone disease*" [3]. He then recounts a succinct history of the early years of collaborative stone research and presentation of data that began in the 7th decade of the twentieth century. We will devote much time and effort now into this historical era of modern stone science. Bichler ends as follows: "*In conclusion, I would like to note that it was and remains a lucky circumstance for our special field that out of the earlier, rather sporadic meetings over the course of time a firm organization: The 'European Urolithiasis Symposium' was founded and built up*

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as a platform for indispensable scientific exchange of ideas. We owe the early activists our sincere gratitude" [3]. These are the foundations of historiography itself, the recordings of past facts upon which the foundations of modern science builds, and the legacy recorded by Sir Isaac Newton himself: "*What Des-Cartes did was a good step. You have added much several ways, & especially in taking ye colours of thin plates into philosophical consideration. If I have seen further it is by standing on ye shoulders of Giants*" [4].

Scientific Meetings and Globalization

The science of stone disease parallels the rising incidence of this disease and the financial burden it has extracted on the communities that are affected by this malady. Both the USA and in particular the European countries were all high-risk regions with progressive scientific interest into the stone-forming events. Organized interest in the scientists involved in various aspects of stone disease first arose about 40 years ago in combined European urology meetings. They have become known as the Eurolithiasis Society. The first European Symposium on Urolithiasis was held at Leeds, England, in April 1968 and was hosted by Clark, Hodgkinson, Nordin, and Williams [5]. The six primary topic areas for research discussion are as follows: inhibitors (pyrophosphate, citrate, magnesium, macromolecules), activity products (Robertson), hypercalciuria, organic matrix (Boyce), nephrocalcinosis (Anderson), and stone analysis [5]. These European meetings became nearly yearly and continue to the present time as the European Symposia on Urolithiasis, also called EULIS. The subsequent meetings were held throughout Europe through the years, bringing together the leading researchers on stone disease throughout Europe to discuss cutting-edge stone research (Table 29.1) [3].

Table 29.1 European Symposia on Urolithiasis locations where meetings occurred

Number	City/location	Year
Prodromal	Leeds, England	1968
	Bonn-Wien—1972, Madrid—1976, Davos—1976, Tel Aviv—1980 (forerunners to current meetings)	
1	Bonn, Germany	1989
2	Basel, Switzerland	1990
3	Madrid, Spain	1991
4	Tübingen, Germany	1993
5	Manchester, England	1994
6	Stockholm, Sweden	1995
7	Paris, France	1997
8	Parma, Italy	1999
9	Rotterdam, The Netherlands	2001
10	Istanbul, Turkey	2003
11	Coburg, Germany	2005
12	Lisbon, Portugal	2007
13	Cancelled b/c IUS in Nice	2008
14	Como, Italy	2009
15	Dusseldorf, Germany	2010
16	London, England	2011
17	Cancelled b/c IUS in Brazil	2012
18	Copenhagen, Denmark	2013

The next meeting occurred in the university town of Jena, called the Jenaer Harnstein Symposium in 1970. This meeting would spawn several more future meetings centered upon the university at Jena with Professor E. Hienzsch and Dr. H.-J. Schneider leading this group and the meetings [6]. Basic urine crystalline chemistry, stone analysis, infectious stone disease, and basic physiology of the upper urinary tract were leading discussions at these meetings. This was followed by the next major international symposium in Bonn-Vienna in 1972. This meeting was hosted by Professor W. Vahlensieck and Dr. G. Gasser from the University of Bonn, November 24–25, 1972 [6]. This symposia in turn resulted in thirteen further meetings and five published Proceedings, largely German that alternated between Bonn and Vienna until 1987 [3]. It was during these symposia that an Advisory Board was formed to plan future European Urinary Stone Symposia [3] (Table 29.2).

Now the stage was set for a truly collaborative European effort. The Advisory Boards would see to it that planning future meetings would proceed in an organized and regular fashion. Gasser concluded his remarks at the 13th

Table 29.2 Members of the Advisory Board of Urinary Stone Symposium developed from the Bonn-Vienna Symposia [3]

Prof. Dr. L. Andersson, Stockholm
Prof. Dr. K. H. Bichler, Tübingen
Prof. Dr. O. Bijvoet, Leiden
Prof. Dr. B. G. Danielson, Stockholm
Prof. Dr. J. Pinter, Debrecen
Prof. Dr. Cifuentes Delatte, Madrid
Prof. Dr. P. Deetjen, Innsbruck
Prof. Dr. H. J. Dulce, Berlin
Prof. Dr. H. Fleisch, Bern
Prof. Dr. R. Hautmann, Aachen
Prof. Dr. G. Gasser, Bonn
Prof. Dr. W. Lytzeyer, Aachen
Prof. Dr. A. Preisinger, Wien
Dr. W. G. Roberstons, Leeds
Dr. G. A. Rose, London
Prof. Dr. G. Rutishauser, Basel
Prof. Dr. H. -J. Schneider, Jena
Prof. Dr. P. O. Schwille, Erlangen
Prof. Dr. W. Vahlensieck, Bonn

Table 29.3 International Symposia on Urolithiasis and Related Clinical Research

Number	City/location	Year
1	Basel, Switzerland	1972
2	Davos, Switzerland	1976
3	Williamsburg, Virginia	1980
4	Garmisch-Partenkirchen, Germany	1984
5	Vancouver, Canada	1988
6	Cairns, Australia	1992
7	Dallas, Texas	1996
8	Cape Town, South Africa	2000
9	Hong Kong	2004
11	Nice, France	2008
12	Ouro Preto, Brazil	2012

Symposium in Vienna with "*Ladies and Gentleman! Though we have been more than satisfied with the results of our urinary stone symposia, we believe, nevertheless, that progress and changes in medicine and in other sciences ought to make likely the enlargement of our basis to European dimensions*!" [3]. The researchers and clinicians would begin to organize and present their cutting-edge work in a timely and methodical fashion, insured as well for an outlet for publication. The Proceedings of these meetings would then also find an outlet of readership. Scientific peer-reviewed journals would also become interested in further publishing pieces of the works presented. Now the European Symposia on Urolithiasis and the every 4-year effort the International Symposia on Urolithiasis were capable of being planned and executed. The European Symposia is now up to its 17th annual meeting (Table 29.1), whereas the 12th International Symposia just held its meeting in Ouro Preto, Brazil (Table 29.3).

The R.O.C.K. Society

Now let's turn to the USA and the organization that would recapitulate what was going on in Europe and internationally. According to archival records which were painstakingly kept by the past President Floyd Fried, the early historical moments of the R.O.C.K. Society have been reconstructed. This acronym stands for *R*esearch *o*n *C*alculous *K*inetics and supposedly was proposed at the Annual American Urological Associations meeting in May 1978. In the USA, acronyms quickly take hold of most things that involve the US government, and a specialty society devoted to urolithiasis research should not be immune. The origins of this group of research and clinical specialist were derived from the National Institutes of Health (NIH) funding for urolithiasis research grants that funded five programs [7]. These SCOR (specialized centers of research) centers were Dr. Broadus from Yale University, Dr. Fred Coe from the University of Chicago, Dr. Bird Finlayson from the University of Florida, Dr. Charlie Pak from the University of Texas Southwestern, and Dr. Lynwood Smith from the Mayo Clinic [7]. These leaders in American urolithiasis were all part of the founding fathers of the R.O.C.K. Society which held its first meeting in 1978 at Covington, Louisiana, home of the primate center for research. George Drach relates that the initial meetings followed the National Kidney Foundation meetings, hence the first meeting in New Orleans in November 1978 with the actual R.O.C.K. Society meeting being held at the Delta Primate Center hosted by Dr. James Roberts [7]. It was here that the constitution and bylaws were generated [7].

The agenda for this group from the inception was to include a broad group of intellectually diverse research folk that were interested in urolithiasis. Quoting Drach, "*the main object for the Society shall be to further the investigation of calculi and reach a better understanding of the basic mechanisms involved as follows:*

1. *By informal group discussion of material that is of cross-disciplinary interest.*
2. *By exchange of ideas pertaining to clinical experiences and experimental research.*
3. *Every member is required to give a presentation at a meeting every three years, or he/she is excluded from the membership in the Society [sic].*
4. *By consideration of problems encountered in calculous research.*
5. *By the promotion of good fellowship and mutual trust among members of this organization*" [7].

Initially the membership was restricted to the North American continent, and members were expelled for missing two consecutive meetings. The spirit and camaraderie that existed in these early meetings is hard to describe, though the author's first experience was in 1989. The small specialized contingent of members did give the meetings an informality that promoted lively discussion of basic and clinical research topics. Most of the members have gone on to become significant leaders in the field of urolithiasis research and the origins of endourology—the terms for minimally invasive urologic surgery that originally focused upon stone disease. The millennial meeting was hosted by the author of this textbook in Albany, New York, on the eve of the US Presidential Election (Table 29.4). As is often the custom at such meetings, a keynote speaker gives an address that might not follow the theme of urolithiasis research. That year the Society heard about the qualities of American President's that make them great from a presidential scholar at the Rockefeller Institute of Politics. It is of the historical interest that of the five

Table 29.4 R.O.C.K. Society annual meetings

Number	City/location	Year	Chairperson
1	Covington, Louisiana	1978	James Roberts
2	Dallas, Texas	1979	CYC Pak
3	Chicago, Illinois	1980	Fred Coe
4	Gainesville, Florida	1982	Birdwell Finlayson
5	Salt Lake City, Utah	1983	Birdwell Finlayson
6	Tucson, Arizona	1984	George Drach
7	Richmond, Virginia	1985	Vernon Smith
8	Rochester, Minnesota	1986	Lynwood Smith
9	Sturbridge, Massachusetts	1987	Mani Menon
10	Chapel Hill, North Carolina	1988	Floyd Fried
11	St. Louis, Missouri	1989	James Gregory
12	Minocqua, Wisconsin	1990	Neil Mandel
13	Cleveland, Ohio	1991	Martin Resnick
14	Dallas, Texas	1993	Glen Preminger
15	Birmingham, Alabama	1994	John Burns
16	Charlottesville, Virginia	1996	Allen Jenkins
17	Steamboat Springs, Colorado	1997	P.J. Chandhoke
20	Gainesville, Florida	1999	Saeed Kahn
21	Albany, New York	2000	Michael Moran
22	San Antonio, Texas	2002	Steven Streem
23	Wrightsville Beach, North Carolina	2003	Ross Holmes
24	Gainesville, Florida	2004	Marguerite Hatch
25	Chicago, Illinois	2005	John Asplin
26	Vail, Colorado	2006	Hari Koul
27	Dallas, Texas	2007	Margaret Pearle
28	Durham, North Carolina	2008	Pei Zhong
29	Los Angeles, California	2010	Gerhard Fuchs
30	Boston, Massachusetts	2011	Gary Curhan
31	Indianapolis, Indiana	2012	James Lingeman
32	Cleveland, Ohio	2013	Manoj Monga

Also beginning in 1997, the R.O.C.K. Society has been meeting biannually, once also at the Annual American Urological Association Meeting in addition to their primary meeting venue original SCOR sites that contributed presidents to the R.O.C.K. Society, all survive and continue as leaders in the field of urolithiasis research except the one that never fostered a president, Yale University.

Stones: An Overview

Stone disease has undergone many alterations in both incidence and prevalence over the past recorded history of this disease (see Chap. 2). Less is known about the alterations of stone type over time, but this certainly has changed as well [8]. Since incidence also includes patients with silent stone disease, the prevalence tends to be significantly lower. According to one large database study (NHANES II and III), the prevalence in the USA has increased from 3.8 % to 5.2 % from 1980 to 1994; this includes all age groups and genders [9]. That said, the most current era began at least in the 1970s when stone researches again noted a rise in prevalence which correlates loosely with the rise of modern stone science and the beginning of collaborative European, international, and US stone symposia. We have looked at stone types, also in the second chapter, and will review each of the major five stone types following this introduction in order of their historical identification as follows: uric acid, calcium phosphate, calcium oxalate, struvite, and cystine stones. We have skipped major discussions of endemic bladder stones because we have covered bladder stones extensively throughout the history. The dietary causes were also discussed in sections regarding epidemiology. Risk factors however are identifiable for stones, and these include age, gender (perhaps less important in modern societies—see next Chapter), geographic location (this too is changing), ambient temperatures, genetic factors, associated diseases, diet (which is also cultural), BMI, hydration, relative water hardness (always controversial), race, and socioeconomic status. In years past, the USA had ranked as low as 17th in incidence but now has arisen to in the top five countries for stones. The peak incidence of stones has always been in the most productive years of one's life in the mid-40s, but the US trends show this too is perhaps shifting to the right, along with our aging population [10]. We will discuss some unique aspects of urolithiasis in the aging population in the concluding discussion at the end of this chapter.

In each of the sections that will follow on specific stone types, attempts will remain to keep this information into a historical perspective. That is to say, the important historical landmarks that lead us to our current state-of-the-art knowledge will be the primary emphasis. So, for instance, in the uric acid stone disease section, there will be a great deal of digression into the fundamental physiology because the historical roots are rather broad and diverse. Certainly knowledge in each of these domains of stone disease is the subject of whole treatises in their own right in terms of modern scientific knowledge. Hence, the focus of this book on historical subjects represents the main theme.

Uric Acid Stone Disease

Stone disease has afflicted humans since before recorded time. We have encountered already an early stone, a bladder calculus, which was well described by Shattock as a fifth-century B.C. Egyptian youth of about 7 years of age. The stone was a mixture of uric acid and struvite. Uric acid was of primary interest to the founding fathers of chemistry [11]. Urinary stones were quite common at the close of the nineteenth century when the founders of chemistry were investigating basic chemical composition, so it is quite natural that they turned their attention to stone disease. Uric acid stone formation represents one of the more fascinating enigmas of chronicled human diseases. Hippocrates (460–370 B.C.) noted the clinical features of gout, its hereditary nature, and male predominance. Gouty tophi and uric acid bladder and kidney stones had been identified. Galen (131–201 A.D.) proposed relationships between gout and urolithiasis [12]. Paracelsus (1493–1541) believed stones were caused by dietary excesses [13]. Thomas Sydenham (1624–1689) suffered from kidney stones and gout. He hypothesized that specific increase in excretion of a kidney stone-producing substance resulted in precipitates of stones. Sydenham's insight is shown as follows: "…*the gout breeds the stone in the kidney of many subjects either (1) because the patient is obliged to lie long on his back, or (2) because the secretory organs have ceased performing their proper functions; else (3) because the stone is formed from a part of the same morbific matter*" [14]. Sir William Osler (1849–1919) followed in the lineage of great medical minds that suffered from urolithiasis. In his first edition of The Principles and Practice of Medicine, his magnum opus, Osler specifically refers to chemical varieties of calculi: "*Uric acid, by far the most important, which may form the renal sand, the small solitary, or the large dendritic stones*" [15].

Uric acid was the first urinary stone constituent that had been successfully identified. In 1776, Karl Wilhelm Scheele (1742–1786) in seminal studies on bladder stones noted that though barely soluble in water, they turned litmus paper red and thus were acidic. Upon heating, the stones produced an odor of prussic acid. He gave the name lithic acid to the substance and thought that all urinary stones were of similar chemistry [12]. In 1795 George Pearson (1751–1828) influenced by both Cullen and Black presented an investigation of 300 stones from the collection of Mr. Heaviside. With exquisite attention to detail, he concluded that lithic acid is not present in the stone but was an oxide. Pearson suggested in his paper to change the name to uric acid, in agreement with Fourcroy who coined the term [16]. Pearson begins his treatise with a history of names in ancient languages that relate to urolithiasis. He goes through a rather complete history of stone formation up until his time spending a good part of it on the alchemists Paracelsus and van Helmont. He then gives credit to Scheele of Sweden who truly identified the importance of an organic acid and the controversies that pulled Lavoisier and ultimately Fourcroy into the chemistry of this compound. I would like to give his summary comment for historical purposes, "*Dr. Link, in a very elaborate dissertation, published at Gottingen, in 1788, on urine and calculi, concludes that urinary concretions consist of phosphoric acid, lime, ammoniac, oil, the bases of different gazes, together with the acid sublimate of Scheele, although he did not succeed in obtaining it*" [16]. Pearson suggested in his paper to change the name to uric. Pearson further points out that most stones do contain uric acid (194/200) but in varying concentrations [16]. Antoine F. Fourcroy (1755–1809) also experimented upon a large number of uroliths and tended to agree with the misconceptions of Scheele. Fourcroy is considered the father of clinical chemistry. His insightful investigations included questioning whether uric acid was confined to humans, if uric acid existed outside of the urine, how it was formed, and if there was any left in the urine after stone precipitated [12]. He proposed and probably performed the first multicenter investigation of environmental and geographic regions to see if different stone types were seen in different areas. Fourcroy and his colleague, Nicolas Louis Vauquelin, not only expanded the chemical properties of uric acid; they identified the sodium and ammonium salts. Fourcroy also pursued the therapeutic possibility of dissolving such stones and commented that only pure uric acid stones should be capable of being dissolved [17].

William Hyde Wollaston (1766–1826) was another contemporary of these other investigators who also was interested in stone chemistry. He also did some early chemistry of both uric acid stones and the gouty concretions of joints [18]. He in this paper names the stone types each by their chemical composition and properties as follows: lithic acid (keeping Scheele's terminology), fusible calculus ("*always whiter than those described by Scheele*"), the mulberry calculus ("*irregularly knotted surface and dark colour, bear a distant resemblance to that fruit*"), bone-earth calculus (pale brown "*phosphorated lime*"), and prostate calculus which he notes are distinct [18]. Wollaston has not got his hands upon the first cystine stone at this time. The rigorous method of experimental pursuit by these early investigators included experiments and dissection of various animal species. They noted that man was the only mammal to form uric acid stones. Pearson and Vauquelin could not find uric acid stones in large carnivores (lions and tigers). Fourcroy followed up these observations by confirming a lack of uric acid stones in the horse, cow, rabbit, dog, cat, pig, and rat [17]. A contemporary of Wollaston was Alexander Marcet. He too was a physician and chemist, working in London and obtaining calculi from Norwich Hospital. He was the first to discover xanthine stones. His book *An Essay on the Chemical History and Medical Treatment of Calculous Disorders* in 1817 was encyclopedic of the knowledge of stones at the time [19]. They were the pioneering fathers of calculous disease and serve a fitting introduction to the discussion of uric acid stone disease which first garnered attention of emerging science.

Uric acid is the end product of human purine nucleotide metabolism. As such, uric acid is far from an ideal end product because it is poorly soluble. In excess, uric acid can precipitate as sodium hydrogen urate (common in joints and tissues) or as uric acid, sodium urate, or ammonium urate in the urinary tract. Man is continually on the precipice of crystallization and precipitation as the urine is relatively supersaturated with uric acid with an average of 600 mg/day [20]. Human uric acid handling has become a complex physiologic issue. Humans lack the enzyme uricase that nearly all other species have to oxidize uric acid into the more soluble allantoin. Uric acid is a weak acid with the hydrogen atom at position 9 of the imidazole ring easily dissociated in the physiologic range (pKa1= 5.75) [21].

A huge literature is available regarding the physiology of purines and pyrimidines. These nucleic acid precursors form the foundations of understanding the physiology of this disease. In fact, if not for the lack of a single enzyme, uricase, human diseases such as gout and uric acid stone disease would not exist. As noted by our forefathers, among mammalian species, only humans and the great apes excrete uric acid as the end product of purine metabolism. The net production of uric acid comes from two primary sources, dietary ingestion and the endogenous production via nucleotide synthesis. This process appears to be most active in liver cells but occurs in all living cells. The synthesis of purines is a sequence of ten enzymatic steps by which small precursor molecules are placed into a purine ring synthesized on ribose phosphate. These small molecular species include glutamine, glycine, and formate to form 5-phosphoribosyl pyrophosphate (5-PRPP), the backbone of the molecule. This high-energy molecule is then involved in purine synthesis in two ways: it combines with L-glutamine and proceeds through de novo synthesis, or it participates in the salvage of purine bases, which can be reconverted to ribonucleotides. The enzymatic process of combining 5-PRPP and glutamine uses the enzyme 5-PRPP amidotransferase that is the major step in the pathway and subject of feedback control. Phosphoribosyl-n-amine is the highly labile amino sugar product of this reaction, and it is converted to inosinic acid (IMP) in a series of 8 steps using glycine. There is little evidence that the intermediates along this pathway accumulate during synthesis. IMP can then be converted to adenylic acid (AMP) and/or guanylic acid (GMP), both of which are essential to DNA and RNA synthesis. Both AMP and GMP can feedback on the control of 5-PRPP amidotransferase limiting production. IMP can also be catabolized to inosine by a specific 5'-phosphomonoesterase and nonspecific acid and alkaline phosphates. This is a costly pathway in terms of energy utilized, requiring 6 moles of adenosine triphosphate (ATP) for generating one mole of inosinic acid, and the first precursor. Purine interconversion is a built-in method of conserving energy and complexly allowing this pathway to reuse preformed purines. The hydrolysis of nucleoproteins and free purines from the diet can be reutilized in the formation of mononucleotides. This obviously is the result of the reversal of the reactions. The enzyme hypoxanthine-guanine phosphoribosyltransferase (HPRTase) catalyzes the transfer of ribose-5-phosphate from 5-PRPP to hypoxanthine and guanine to form IMP and GMP, respectively. HPRTase activity is also subject to negative feedback inhibition by IMP or GMP, and APRTase activity is inhibited by AMP excess.

There are hereditary syndromes of enzyme deficiency that can disrupt this reutilization pathway. Lesch-Nyhan syndrome is an HPRTase deficiency associated with very high incidence of uric acid stones, interstitial nephritis, and neurological syndrome of choreoathetosis, mental retardation, spasticity, and self-mutilation. Enzyme deficiencies have been described for APRTase activity and the association of 2,8-dihydroxyadenine stone formations [12].

The last step in the production of uric acid involves xanthine oxidase degradation of hypoxanthine and xanthine to uric acid. This enzyme is rather indiscriminate and acts upon a host of substrates. The liver and the small bowel have the highest concentrations of this enzyme, but the kidney, spleen, skeletal muscle, and heart have activity. Hereditary deficiency in xanthine oxidase has also been discovered. These patients excrete xanthine and hypoxanthine as the end products of purine metabolism. Xanthine is less soluble in urine than is uric acid, and these patients suffer from recurrent xanthine stone formation [12].

The primary determinant of uric acid solubility is the pH of the urine. At a pH of 5, uric acid solubility is 8 mg/dl; at a pH of 7.0, it is 158 mg/dl. The first pKa of uric acid is variously quoted from 5.35 to 5.75.8 In a graph of the dissociation curve for uric acid, the urine pH on the abscissa, the percent of total uric acid as free undissociated uric acid on the ordinate, and a pKa of 5.57. At this point, 50 % of the total uric acid is free. The second dissociable proton has a pKa about 10.3 and is not normally clinically significant. The solubility of uric acid in urine is different than in water, being modulated by other ions. At a pH of 5.35, only 200 mg/L of urine can be present without exceeding supersaturation. When the urine pH is raised to 6.5, greater than 1,200 mg/L remains soluble.9 Sodium concentration has a significant impact upon the solubility of uric acid. As sodium concentrations rise from 6 to 140 mEq/L, this results in a 20-fold reduction in the solubility of sodium urate. Ammonium urate is also sparingly soluble with only 5.4 mg/dl at a pH of 7.4 [12].

The average adult consumes approximately 2 mg of purine per kilogram of body weight, which results in 200–300 mg of urine uric acid daily. Endogenous production is also about 300 mg/day [22]. Endogenous production comes from de novo synthesis and tissue catabolism and purine reclamation. In studies by Coe, uric acid excretion was estimated to be 5.6 mg/kg/day [23]. Dietary RNA purines contributed 50 % and DNA 25 % of the urinary uric acid. Total uric acid excretion is about 600 mg/day for an average person. Excretion of xanthine and hypoxanthine is normally in the range of 5–10 mg/day [24].

Urinary excretion of uric acid and quantification of the amount varies upon the methods used to collect the specimens, upon the size and gender of the patient, the baseline renal function, and dietary ingestion [25]. Urine collected and stored refrigerated, for example, will have uric acid crystallize and precipitate at the bottom of the container, skewing measurements [26]. Dietary consumption of purine varies from day to day and from person to person. These fluctuations in dietary consumption translate to wide variations in urinary excretion of uric acid [27]. Looking more closely at 24-h urine determinations, Pak in a series of 225 urolithiasis patients on random diets found, by comparing two 24-h urines, a high degree of correlation from one to the other [28]. Of these 225 patients, 27 were uric acid stone formers. Uric acid excretion was 609 ± 214 in the first sample and 597 ± 203 in the second with a % concordance of 84.2, an r of 0.68 ($p < 0.0001$) [28]. They did not break out the 27 uric acid stone formers for separate analysis; however, daily variation was substantial with the 95 % confidence intervals (2 standard deviations) ranging from 101 to 1,097 mg/day. Finally, other factors can affect urinary uric acid levels. This includes the ingestion of alcohol, long associated with gout and uric acid urolithiasis [29]. Fructose ingestion is another potential variable [30]. Obesity has long been linked to disorders of purine metabolism, both gout and uric acid stone formation [31]. A last consideration should be the ability of the intestinal microenvironment to process and catabolize purines. The gut microorganisms are capable of metabolizing purines and possess the enzyme uricase [32]. Uric acid stone formation has also been unequivocally linked to diabetes mellitus, so this stone type might be expected to rise again in incidence with time as this disease is also on the rise in our society of chronic disease states [33].

Calcium Phosphate Stone Disease

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 dihydrogen phosphate. Stones composed predominately of calcium phosphate approximately 10–15 % of the total, and in this stone type, females definitely predominate. Up to 25 % of calcium phosphate stones are calcium dihydrate phosphate (brushite) [34]. Pearson in his 1798 paper on uric acid stones also mentions Bergman and Bewley having noticed calcium phosphates in stones [16]. Wollaston also describes these as bone-earth calculi. He notes that these stones dissolve entirely in marine or nitrous acid, and by heating, they become entirely white [18]. We have already noted that the founding fathers considered calcium phosphate to the nidus of most stones. They became more controversial in the modern era; however, most modern studies do generally confirm that most calcium stones begin as calcium phosphate foci [35]. The physical chemistry of brushite was early investigated by Stokes in 1945 [36]. The group at the University of Chicago followed up these studies by investigating the solubility and experimental role of calcium phosphate in 1958 [37]. Elliot reported upon the metastable limit of calcium phosphate in urine in 1957 [38]. And this was followed by calculated ion-product determinations by Robertson and colleagues [39]. Charlie Pak made some fundamental observations upon the degree of saturation of urine with respect to brushite and anticipating stone recurrence [40]. Pak followed up this study with even more data establishing the primacy of brushite saturation in urines of stone-forming patients as a regulatory role in stone formation [41]. Calcium phosphate-containing stone disease is much more common in secondary diseases that can present with stones such as hyperparathyroidism, sarcoidosis, and distal renal tubular acidosis [42]. Milk alkali syndrome and vitamin D intoxication are also more likely to present with calcium phosphate stone disease [43].

Patients presenting with pure calcium phosphate stones should prompt full metabolic evaluation by the treating physician as these stones represent a harbinger of active metabolic process 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 [44]. In addition, pure brushite calculi represent the second most difficult stone to fragment with SWL, predisposing to secondary interventions [45]. It also appears that calcium phosphate stones are increasing in prevalence in the USA [46]. They conclude this paper with a warning, "*Our study suggests a strong trend for the conversion of stone disease from calcium oxalate to calcium phosphate containing stones, which could influence the progression and severity of disease*" [46]. There is progressive work that suggests that this is indeed happening in our stone patients. In fact Parks and colleagues go further, "*It is therefore worrisome that we and others have noted an increase in prevalence of CaP in stones over the past two decades*" [47]. The concern is for the tubular damage that is associated with calcium phosphate precipitation in the papillary tubules [48]. Shock wave lithotripsy-induced renal tubular damage has also been implicated in the increased prevalence in calcium phosphate stones in some patients. Since calcium phosphate is associated with alkaline urine or a higher pH, attempts at modifying the urine pH by chronic acidification have been attempted. In a long-term follow-up study on a small number of patients that included some struvite stone formers, they did note a trend towards improved urinary acidification though they did not mention the drop out from this small trial [49]. One final note upon calcium phosphate stone formers is that they also have been noted to have significant calcium phosphate crystalluria with fine aggregates and spherules of this crystal excreted primarily as apatite [50].

Calcium Oxalate Stone Disease

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 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 ± 7 % of all stones [51]. This is also the mulberry calculus identified by Wollaston: "*This stone, though by no means overlooked, and though pointed out as differing from other species, has not, to my knowledge, been subjected to any farther analysis than is give, in the Second Volume of the Medical Transactions, by Dr. Dawson, who found that his lixivium had little or no effect upon it; and in the Phil Trans by Mr. Lane, who, among other simple and compound stones, give an account of the comparative effects of lixivium and heat upon a few specimens of mulberry calculus; but neither of these writers attempted to ascertain the constituent parts*" [18]. He goes on to describe the numerous chemical properties that make calcium oxalate unique.

Hypercalciuria is the most dominant finding in patients with calcium oxalate stone disease, and this has been known for some time [52]. Hypercalciuria has been identified in as much as 60–70 % of calcium oxalate stone formers. The term idiopathic hypercalciuria was coined by Fuller Albright's group at Massachusetts General Hospital in 1953 [53]. Calcium increases the ionic activity and saturation of crystallizing calcium salt in human urine. Charlie Pak classified these subdivisions by measurable differences responding to calcium challenge as follows [54]:

Absorptive hypercalciuria type I—non-dietary responsive intestinal absorption of calcium (PTH suppressed)

Absorptive hypercalciuria type II—dietary responsive intestinal absorption of calcium (PTH suppressed)

Absorptive hypercalciuria (phosphate leak, type III)—absorptive hypercalciuria associated with renal wasting of phosphorous. Renal hypercalciuria—renal leak of calcium (PTH stimulated)

Resorptive hypercalciuria—secondary to increased bone demineralization (primary hyperparathyroidism)

The primary defect in absorptive hypercalciuria is an increased passive mucosal absorption of calcium and oxalate in the jejunum. There are strong indications that this defect is autosomal dominant, making a family history of calcium stone disease a risk factor. This may be a vitamin D3-mediated process since up to 50 % of patients with absorptive hypercalciuria have elevated 1,25-dihydroxyvitamin D levels. A recent review of this stratification of hypercalciuria shows that 20 % have type I, 28 % have type II, 2.5 % had renal type, and 3.5 % had resorptive type [55]. Not all investigators are convinced that such stratification is appropriate and that all hypercalciurias are derived from intestinal calcium reabsorption disorders. In fact, it is now believed that these pathways all probably overlap within a range of combined bone and gut abnormalities [56]. The genetics of these interactions and the link to familial tendencies will be presented separately towards the end of this chapter.

Several other identifiable abnormalities of urinary ions offer insight into the pathophysiologic mechanisms of urolithiasis formation. Hypocitraturia is another physicochemical abnormality associated with stone formation in 15–63 % of patients [57]. Urinary citrate levels should typically be greater than 320 mg/day. Conditions associated with hypocitraturia are multiple including distal renal tubular acidosis, chronic diarrhea, laxative abuse, or idiopathic [58]. Hyperoxaluria is noted in 5–15 % of stone series. There are three main groups of hyperoxaluria: inborn errors in the metabolism of oxalate synthesis, increased substrate provision from dietary-rich foods, and increased intestinal absorption (either secondary to surgery or secondary to loss of gut bacteria such as *Oxalobacter formigenes*) [59]. The ability of this gut organism to be manipulated to the advantage of patients with hyperoxaluria or even in calcium oxalate stone formers with just borderline hyperoxaluria is subject to research scrutiny: "*Oxalobacter interacts physiologically with colonic mucosa by inducing enteric oxalate secretion/excretion leading to reduced urinary excretion. Whether Oxalobacter, or products of Oxalobacter, can therapeutically reduce urinary oxalate excretion and influence stone disease warrants further investigation in long-term studies in various patient populations*" [60]. Eighty percent of urinary oxalate is from endogenous sources, whereas 10 % is dietary. Primary hyperoxaluria type 1 is caused by a deficient liver enzyme. Type 2, or l-glyceric aciduria, is a much rarer variant [61]. Enteric hyperoxaluria occurs in patients with derangements of small bowel absorption such as jejunoileal bypass, small bowel resection (short gut syndromes) with or without steatorrhea [62]. Idiopathic hyperoxaluria makes up the remainder of patients with elevated urinary oxalate levels greater than 40 mg per day and probably represents the vast majority of patients with slight elevations in urinary oxalate excretion. Hyperuricosuria has been noted alone or in combination with one of the aforementioned metabolic abnormalities in 10–50 % of stone formers. The increased urinary excretion of uric acid (>600 mg/24 h) on restricted diets is diagnostic [22]. There are other measurable active ions present in the urine that can have an effect on stone risks. These include common substances such as sulfate and ammonium and trace elements such as cadmium or lead.

The previous discussions should lead the reader to understand the complexity of categorizing patients with urolithiasis. In one paper, Pak and colleagues have identified 14 metabolic causes of calcium stone formation [63]. In other series, many if not most patients with calcium stones have more than one risk factor for stone formation. It should therefore be no great surprise that the coexistence of bone loss with the presence of calcium stone formation is controversial but increasingly suspected in patients with long-standing urolithiasis [64]. The different causes of stone formation, particularly the hypercalciurias, not only vary widely from patient to patient but significant variability of hypercalciuria can also be noted within the same patient from day to day [65]. Fournier and colleagues point out that different densitometry methods employed in various published series do not always use standardized parameters and biochemical markers of bone remodeling [66].

Calcium is the most abundant mineral in the human body, accounting for 1.5 to 2 % of an adult's body weight. 99 % of the body's calcium is found in bones and teeth complexed with phosphate as hydroxyapatite. The remaining calcium is being utilized throughout the body for the biochemical processes necessary for life. Bone is therefore an important reservoir for calcium and constantly being turned over. Throughout the human life cycle, there are 3 phases of bone growth and development. From birth to about age 20, the bones are in an active growth phase. Here bones are shaped and molded. This phase is overlapped by a phase of peak bone mass development from ages 12 to 40. Between the ages of 30 and 40, bone resorption begins, resulting in a net loss of bone [67]. Bone mass itself is influenced in turn by many factors including physical activity, gonadal hormones, and nutrition [68]. People of all ages and with a wide variety of comorbid medical problems such as urolithiasis need dietary calcium to maintain positive calcium balance. The Committee on Dietary Allowances of the Food and Nutrition Board, National Academy of Sciences, periodically evaluates research data and furnishes guidelines called Recommended Dietary Allowances (RDAs). Published RDAs for calcium are shown in evolution over time in Table 29.1. The 1994 Consensus Development Conference resolved that the contemporary calcium requirement for both men and women is too low for optimal bone health [69].

Various bone densitometry methods have been employed for study bone loss in patients with calcium urolithiasis. Fournier and colleagues tabulated the world's literature to state that calcium stone formation adversely effects bone mineral density [66].

The exception are those patients with absorptive hypercalciuria type I. Patients with dietary calcium-dependent hypercalciuria (type I) do not have more progressive bone mineral loss than age-matched controls. The patients with absorptive hypercalciuria and phosphate leak (type III) are the most likely to have bone mineral loss. The familial aggregation of this particular type of stone former has prompted numerous genetic investigations regarding the etiology of this disease. It appears that the heterozygous mutations of NPT 2a gene are a result of a sodium phosphate cotransporter are the culprit [70].

As evidence mounts as to the potential for long-term sequelae of bone mineral loss in calcium stone formers and the potential for a protective effect by dietary calcium intake, prudent recommendations suggest not limiting calcium intake [71, 72]. In addition to potential deleterious effects upon the bone, dietary restriction of calcium can result in increased oxalate absorption [71]. Because of the prevalence of osteoporosis, 25 million people in the USA, and the fact that it is the major underlying cause of bone fractures in postmenopausal women and the elderly, loss of bone mineral density is a significant consideration. Surveys have revealed that 1.5 million fractures annually in the USA produce a $10 billion expenditure for our health-care system [69]. Compared to the 1986 fiscal impact of dealing with stone patients surgically, $2 billion, the impact in the USA alone is staggering [73]. Perhaps truly efficacious medical, fluid, and dietary therapies are the keys to lowering the staggering financial effect of stone disease on health-care costs [74].

Struvite Stone Disease

Magnesium ammonium phosphate hexahydrate (struvite) are the bacterial-induced or infectious stones. These stones are often heterogeneous with varying amounts of other mineral (carbonate apatite) or proteinaceous matrix present. These stones represent 2–20 % (Table 29.5) 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. They also were described in some detail by Wollaston in 1797 [18]. He called them fusible calculi: "*My next subject of inquiry has been a species of calculus, that was first ascertained to differ from that of Scheele by Mr. Tennant; who found that when urged by the heat of a blow-pipe, instead of being nearly consumed, it left a large proportion fused into an opaque white glass, which he conjectured to be phosphorated lime united with other phosphoric salts of the urine, but never attempted a more minute analysis*" [18]. He goes on to describe the basic crystals which "*consist of phosphoric acid, magnesia, and volatile alkali: the stone contains also phosphorated lime, and generally some lithic acid*" [18]. He states the crystals are "*short trilateral prism, having one angle a right angle, and the other two equal, terminated by a pyramid of three or six sides*" [18]. In 1885 Hauser described a unique member of the *Enterobacteriaceae* called *Proteus*, named after the shape-shifting demigod of the Odyssey, the old man of the sea [75]. Though there are now five named species of the genus *Proteus,* they all have the characteristic of "*changeability of form, as personified in the Homeric poems in Proteus… and has the gift of endless transformation*" [76]. Though E. coli is the most common pathogen in the urinary tract, Proteus infections rank third in about 3 % of UTIs [77]. The enzyme urease is produced by *Proteus* species and several other bacteria including *Providencia stuartii*,

Table 29.5 Comparative incidences of forms of urolithiasis

Form of urolithiasis	Incidence in the USA (%)
Pure calcium oxalate stones	33
Mixed calcium oxalate and phosphate	34
Pure calcium phosphate	6
Magnesium ammonium phosphate (struvite)	15
Uric acid	8
Cystine	3
Artifacts and others	1

Haemophilus influenzae, *Bordetella pertussis*, *Bacteroides corrodens*, *Yersinia enterocolitica*, *Brucella* spp., *Flavobacterium* spp., some types of *Staphylococcus aureus*, *Corynebacterium* spp., *Micrococcus varions*, and some mycoplasma and yeasts [78]. The urease enzyme is capable of splitting urea into carbon dioxide and ammonia which results in a cascade of chemical reactions leading to formation of struvite crystals identified by Wollaston but named by Georg Ludwig Ulex after finding them in guano deposits.

The association of ureolytic bacteria with infectious kidney stones has been well established soon after finding *Proteus* by Gustav Hauser [79]. Urea hydrolysis creates an alkaline urine pH, causing a precipitation of struvite and apatite crystals. These crystals are entrapped in a matrix of previously uncertain origin which increases in size until severe renal damage may occur [80]. An animal model of an artificially induced bladder infection in rats was enhanced by bacterial strains exhibiting a wide range of urease activity [81]. They concluded that urease activity alone could not explain the pathogenicity of these strains. A number of workers became interested in studying this matrix in more detail. Observations that staphylococci were integrated into the matrix of infection stones led Hellstrom to propose that these bacteria were implicated in matrix formation as well as crystallization [82]. Boyce became interested in infectious stones and analyzed decalcified urinary calculi looking specifically at matrix composition and finding it largely made up of mucopolysaccharides and mucoproteins [83, 84]. They were unable to identify hexuronic or sialiacids which are common in many bacterial exopolysaccharides [85–87]. This may be explained in part by the presence of the renal enzyme, sialidase, which alters these residues. Boyce suggested that matrix deposition was a necessary prerequisite to the stone growth. These findings in turn led back to Vermuelen who hypothesize that the matrix formation occurred solely as a consequence of crystallization processes. As crystal-free regions or "matrix" stones are often found at the periphery of struvite stones, it is likely that matrix formation precedes calcification [81]. Our modern understanding of this complex interaction of matrix and mineral deposition is summarized by McLean's proposed mechanism of stone formation: "*Invading urolytic pathogens such as P mirabilis colonize kidney epithelial cells and form glycocalyx-enclosed micro-colonies. The urease activity of these bacteria creates an alkaline urine, causing precipitation of struvite and apatite crystals. The glycocalyx serves to trap these crystals and other components present in the urine, such as mucoproteins, as well as to protect the pathogens from antibiotics and host-mediated immune responses. As these struvite- and apatite-encrusted microcolonies enlarge into mature calculi, there is an increased incorporation of urinary mucoproteins into the matrix, along with continued bacterial growth, urease activity, and crystal deposition*" [88]. Advanced scanning electron microscopy and energy-dispersive X-ray analysis of this amorphous substance seem to confirm these observations. Microcolonies of bacteria literally envelope themselves in protective layers of glycocalyx which serves to bind struvite (MgNH4PO4 X 6 H2O) and apatite [Ca10(PO4)6CO3] crystals [88]. The mature stone, in effect, represents an enlarged "fossilized" bacterial microcolony.

As many as 25 % of patients with infected stones are asymptomatic, and the stones can therefore grow to quite large proportions, even full staghorn types that fill all of the interstices of the renal collecting system [89]. The patients may become symptomatic when these stones either begin to obstruct or to destroy the renal parenchyma, and then the patients behave like they have pyelonephritis or even more severely like pyohydronephrosis [90]. In severe cases, the renal parenchyma itself becomes involved in the inflammatory process as it is destroyed by invading macrophages producing xanthogranulomatous pyelonephritis [91–94]. Treatment of infectious stones can be primarily medical with phosphate restriction or depletion (phosphate-binding antacids like the Shorr regimen), urinary acidification (ammonium chloride), antibiotics, blocking the enzyme uricase with specific enzyme blockers (hydroxyurea or acetohydroxamic acid), and chemolysis (renacidin or

Suby's solution), but these are typically reserved for postoperative management scenarios trying to lower the high recurrence rates. Priestly and Dunn noted that from 1927 to 1940, the survival rate was 81 % for those who had surgery versus 41 % for those who followed expectantly [80]. We have already reviewed the Blandy and Singh study that compared sixty patients managed conservatively versus 125 treated surgically and that the 10-year mortality rate was 28 % in the former and 7.2 % in the surgical group [95]. Surgery has evolved from the primary open methods which we have already reviewed to less invasive modalities, and these methods apply for the treatment of these complex patients. In the presence of infectious stones, however, remaining fragments are almost synonymous with failure and stone regrowth leading to complex recommendations and the formulation of AUA Nephrolithiasis Clinical Guidelines Panel suggesting combined modalities that achieve about an 80.9 % stone-free rates [96]. Despite all of the aggressive modalities for treating these patients, they tend not to do well over time and represent a higher percentage of stone patient who develop chronic renal failure [97].

Cystine Stone Disease

> *It is an old experience that Nature often grants us through her errors unexpected insights into her secrets, which are otherwise a closed domain* [98].
>
> —A. Loewy and C. Neuberg, 1904

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, ornithine, lysine, and arginine, COLA). Cystine stones are radiopaque secondary to their disulfide bonds. This also makes the incidence of heterozygotes much more prevalent than the homozygotes by at least a factor of 3 (if simple Mendelian inheritance is involved). William Hyde Wollaston was the font of knowledge where this rare stone type was first recognized [99]. His paper, *On cystic oxide, a new species of urinary calculus* is a historical masterpiece. It begins with "*The principal design of the present essay is to make known the existence, and to describe the leading properties of a new species of urinary calculus from the human bladder; but I shall at the same time take the opportunity of correcting an inaccuracy or two that I have observed in my former communication on this subject*" [99]. He is talking about correcting the classification of five types of stones he previously presented: lithic acid, oxalate of lime (mulberry), phosphate of lime (bone-earth), ammoniacal phosphate of magnesia, and fusible calculus (combination of the last two types). He now presents the sad tale of Dr. Reeve of Norwich who presented a portion of a bladder stone removed from his brother who was 5 years old and later died of multiple stone recurrences [99]. In Wollaston's words, "*I am informed, that another stone formed afterwards in the bladder of this boy, and that he died in consequence, without submitting to the operation a second time*" [99]. A second stone was also noted from Guy's Hospital collection (No. 46) obtained from Mr. Lucas (surgeon) coming from William Small aged 36. He notes that "*In appearance, these calculi resemble more nearly the triple phosphate of magnesia, than any other calculus; but they are more compact than that compound is usually found to be: not consisting of distinct laminae, but appearing as one mass confusedly crystallized throughout its substance. Hence, instead of having the opacity and whiteness observable in fusible calculi, which consist of a number of small crystals cemented together, these calculi have a yellowish semi-transparency; and they have also a peculiar glistening luster, like that of a body having a high refractive density*" [99]. He goes on to describe the various unique chemistry properties, and it is noted in the following: "*Under the blow-pipe it may be distinguished from uric acid by the smell, which at no period resembles that of prussic acid; but in addition to the unusual small of burned animal substances; there is a peculiar foetor, of which I cannot give correct idea, as I know no smell which it can be said to resemble*" [99]. He admirably is describing the burned smell of sulfur that every urologist is immediately aware during the laser lithotripsy of cystine stones [100]. Wollaston chose the name "*cystic oxide*" because he believed these stones originated in the bladder in contradistinction to other stones that were felt to have a renal origin. His protégé Marcet, however, quickly identified two cases at autopsy that had renal stones, and he even proposed changing the name to "*nephric oxide*" [17]. Civiale even weighed into the discussion of this stone suggesting the name "*sacrodosmine*" because of the odor like garlic when this stone was burned. Berzelius, like so much of the early history of chemistry, had the final say; he named it cystin, correcting the fact that it was not an oxide: "*Of this new name, which has since been universally adopted, Civiale wrote, in 1838, that although it corrected an error of chemistry it perpetuated an error of physiology, for cystine is excreted by the kidneys and does not have its origin in the bladder*" [101]. First Prout in 1820 and then Strohmeyer in 1824 noticed the same hexagonal crystals in the urine that Wollaston had initially identified from dissolved stones [102].

Early on in this disease process, a familial pattern was noted almost immediately by Marcet. He described two brothers with the disease, only the 4th and 5th cases ever noted [17]. Albert Niemann (1890–1921) wrote the early definitive work on this disease in 1876 while working with his mentor Ebstein whom we've already met. Niemann would ultimately identify Niemann-Pick disease but documented 52 cases of cystine stone disease and described the newly identified nitroprusside reaction as an "*elegant*" test [103]. He also noted the family dispositions well before widespread knowledge of Gregor Mendel's (1822–1884) work on hybridization of peas recently published in 1866 [104]. Niemann wrote "*in unserer Kenntniss über die genetischen Bezichungen der Cystinurie nicht weiter gebracht*." He was anticipating genetics but is far from finished with his observations and speculations about this rare disease (Bateson is typically given credit for discovering the term "*genetics*"). He noted that cystinurics' urine when left standing for days developed an absolutely horrendous odor (he did not know of cadaverine and putrescine metabolism by bacteria). He was the first to note that crystalluria was present even in non-stone-forming cystinuria. He presciently suspected that cystinuria was present from birth based upon his careful observations that these stones presented almost equally in all age groups. He noted no significant gender tendency suspecting that it equally affected both sexes. He also estimated correctly that cystine stone represents 1 % of the stone patients by looking at the data from the Hunterian collection of 3/649 stones and the data from three stone clinics. Niemann also vociferously attacked the leading hypothesis of pathogenesis of cystinuria up till his time that alcoholic liver problems were to blame; he clearly used the infant data to show this was not the case and hypothesized that an "*arrest of metabolism*" might be the cause which again anticipates the work of Archibald Garrod 50 years later with his "*inborn errors of metabolism*" [101]. Ebstein who was no slouch honored his student by republishing his paper 8 years later adding ten new cases to the original 52. In addition, Simon also reprinted Niemann's list with all cases till 1900 now totaling 103 cases [105]. Niemann noted that "*our knowledge of cystinuria has indeed developed unusually slowly and by small degrees*" [103].

We have already noted that members of the Reeve family were carriers of cystinuria in the very first stones identified. Sir Archibald Garrod (1857–1936) coined the term "inborn errors of metabolism" and noted the probable inheritance of cystinuria in 1906 [106]. The rare metabolic condition was certainly present in early America as some of the first surgeons noted this rare form of stone disease. Benjamin Winslow Dudley (1785–1870) and James Mills Bush began to document and record each stone case with chemical identification of the concretion which was performed by the Professor of Chemistry, Dr. Robert Peter. They removed perhaps the first cystine stone in America in the 1840s [107]. The chemical formula of cystine and its reduced form cysteine were identified by Friedman in 1902 [108]. Now scientists knew what they were looking for and a source became readily available when it was found abundantly in human hair [109]. The first metabolic studies utilized the patient's own urinary cystine that was fed back to patients and paradoxically caused no increase in urinary cystine excretion [110]. It was noted that these patients excreted differing amounts of cystine when challenged with dietary sources [111]. They also noted that methionine, not cystine, gave rise to higher excretion than proteins with lower methionine content. They identified the metabolic pathway as follows: methionine > homocystine > cysteine > cystine > sulfate > urinary cystine crystals.

Only the intermediary cystathionine was missing, and this would take radiolabeled assays to identify this and the need for homoserine in the metabolism of sulfur amino acids. Dogs had been identified as occasional cystine stone formers in 1823. Wolves, mink, and the blotched genet (a Kenyan wildcat) have been identified in forming these stones [112]. The other amino acids excreted in patients with cystinuria were identified in a young girl's urine in 1947 [113]. Now the various types of this rare disease had a phenotype that could be evaluated. The ratio of aminoaciduria was identified by Stein in 1951 to be 1:1.2:2:5 for ornithine-cystine-argenine-lysine [114]. Dent and Harris were a research group at the University College in London could now subtype specific aminoacidurias and wrote their classic paper *The Genetics of 'Cystinuria'* in the *Annals of Eugenics* in 1951 [115]. The same investigators were able to measure the renal clearance of these amino acids [116]. Normal cystine clearance was 4 ml/min, heterozygotes were 14 ml/min, and homozygous patients were about 100 ml/min. Cystinuria was a hereditary inactivity of a specific renal transport system related to each dibasic amino acid.

Harris continued this work on urinary excretion of amino acids in 29 families of patients with cystine stone disease. He reported on two distinct phenotypes in 1955 [117]. Type I had greatly increased levels of COLA and formed stones frequently only in homozygotes. Type 2 patients had moderately increased cystine and lysine and formed stones rarely and were called "*incompletely recessive*" [117]. Investigation into complex amino acid clearance in patients with cystinuria was carried out in 1958 [118]. An animal model for the transport of this dibasic amino acid was developed in 1959 [119]. The serum and urinary chemistry of cystine were reported in 1960 [120]. Leon Rosenberg and colleagues at the NIH noted that cystinuria showed various differences of transport of the dibasic amino acids intestinally in 1965 [121]. They followed up on their observed differences and further noted, and three types of genetic phenotypes were known [122]. In the 1970s and 1980s, the amino acid transporter genes were identified, and the actual mutations causing these defects were identified. Also specific mutations and gene frequencies were identified in Libyan Jews with a rate as high as 1/2,500 neonates. The explosion of genetic information has increased at such a rate that there are now 103 different mutations that have been identified in SLC3A1 located on chromosome 2p16.3-21 and 66 in SLC7A9 [123].

The clinical management of cystine stone formers lies in increasing fluid consumption to achieve large volume of urine formation which must be maintained lifelong. The upper limit of cystine solubility is about 400 mg/L, and elegant studies on supersaturation have been completed [124]. Dietary restriction of high-methionine foods (low to moderate protein intake) and restriction of salt intake are also generally recommended. The role of urinary alkalization has been controversial, but generally recommended (the pKa of cystine is 8.5 and unachievable in humans), and the risk of converting patients into calcium phosphate-producing stone formers is always a risk. There is a propensity for these stones to occur in younger individuals, 2nd to 3rd decades, and two-thirds are pure, whereas one-third contain a mixture with a mineral content [125]. Binding the sulfhydryl group on the cystine molecule has resulted in several drugs that increase solubility of this amino acid. Captopril is a weakly binding agent, but doses need usually to be high for any efficacy producing untoward side effects. D-penicillamine was a chelating agent that became available in the 1960s [126]. The binding complex was 50X more soluble than cystine itself, but toxicities, sometimes fatal, were common and as many as 2/3 of patients were unable to continue taking this medication [126]. Alpha-mercaptopropionylglycine (α-MPG) was thought to be an improved thiol binder but side effects were still common, but the percentage that had to discontinue the drug fell to about 30 % [127]. A dithiol binder called bucillamine (Rimatil) has recently been described which might have lower toxicity, but little clinical data is available [128].

Associated Diseases

The complexity of stone disease and the prophetic statement of Alexander Randall that stone disease does not exist, stones are a symptom or a product that results from a final common pathway of some disease processes [129]. He was correct in most of his hypothetical thought processes, perhaps a bit dogmatic on his terms "*origin*," but we shall now explore the literal explosion of new ideas that resulted in urolithiasis formation in relationship to other diseases. Albright also was correct, and he too was prophetic in his skepticism of the word "*origin*" as well [43]. His pioneering efforts in early American physiology produced a legion of others who also followed disease to the stones that patients would develop.

Early in the clinical literature of urolithiasis, it was documented that humans who are incapacitated and bedridden are prone to kidney stones. In 1922, Paul from Toronto reported on 20 cases of nephrolithiasis occurring in men aged 22 to 37 (average 28.5) who developed renal calculi following war wounds. The average time from the wound to the first symptoms of stones was 17.7 months. All patients had extensive injuries including osteomyelitis. Most of these patients were bedridden for prolonged times [130]. Fowweather followed by Pulvertaft indicated that recumbency appeared to be the critical problem associated with calcium stone formation, not the degree of trauma [131, 132]. The primary event increasing the risk of nephrolithiasis appears to be an acute mobilization of calcium from the skeletal reserves [133]. In some patients, hypercalciuria may be pronounced [134]. In these patients, indwelling Foley catheterization is also common, and subsequent bladder infection makes upper tract seeding commonplace. Recurrent urinary tract infection therefore changes the primary stone risk in these patients with high urinary pH with the potential for ammonium production to form struvite stones (magnesium ammonium phosphate hexahydrate) [135]. In current practice with the emphasis on early mobilization and vigorous rehabilitation, no patients except perhaps those with global trauma (i.e., multiple organ injured individuals) run this risk. One current investigation on immobilization-related hypercalcemia of a mere 5 patients suggest that we can alter bone mineral loss [136]. In this entire immobilized group, the hypercalcemia during three months of observation could be reversed by administration of low-dose pamidronate (10 mg). In a review by Gordon and Reinstein, a discussion of common secondary problems associated with the management of complex trauma victims revealed the urolithiasis was a significant problem. In addition, the costs in managing this secondary problem was significant [137]. It would seem reasonable, despite a paucity of published data, that immobilized patients are at higher risk, and maintenance of adequate hydration would be a minimal recommendation. The use of bisphosphonates is more uncertain but indicated if hypercalcemia or urolithiasis develops.

Another consideration regarding the effect of physical activity on calcium balance, calcium requirements and upon bone mineral mass and the effect on stone formation is age. Because of the aging population and the increasing risk of osteoporosis-induced risk of presbic fractures, a significant volume of research is becoming focused upon these issues. In some studies, physical activity has been noted to have a more profound role in affecting enhanced bone mineral density prior to puberty [138]. The need for greater research and the potential for physical activity itself to have an effect upon calcium balance are critical [139].

A correlation between stone development and bowel disease, specifically chronic diarrheal syndromes, has been known since Lindahl and Bargen published in 1941 [140]. Chronic diarrheal illnesses have been well investigated since the 1940s, and the prevalence of stone disease has been reported. Each of the types of inflammatory bowel disease appears to have a relative impact on stone formation. Worcester, in an extensive review of published series, has tabulated the prevalence of stones for patients with Crohn's disease and ulcerative colitis and in those patients requiring bowel and/or ileal resections [141]. There are many complicating issues in these patients including duration of disease, hydration, use of medications such as steroids and sulfasalazine, and disease-specific problems that directly impinge upon the urinary tract (such as retroperitoneal abscess, ureteral obstruction, and vesicoenteric fistulae). Stone prevalence in Crohn's disease is about 6.3 % (range 3–8 %). In ulcerative colitis, the rate is 4.4 %. Worcester further approximated that these high-risk patients are further stressed about 3× higher by having bowel surgery [142–144]. In a modern large review of Crohn's patients, a survey of 7,210 patients in Germany found a 19.6 % return rate of questionnaires (1,414 patients). Of these, it was noted that 17.2 % had a urinary calculus dwarfing previous expectations [144].

Sarcoidosis is a systemic granulomatous disease of unknown etiology. Hypercalcemia varies from 2 to 63 % of patients with sarcoidosis. This hypercalcemia has classically been ascribed to vitamin D formation when it was initially noted 6 of 11 patients with this disease [145]. Henneman and colleagues noted that the calcium disorder of sarcoidosis was similar to vitamin D intoxication [146]. About 5 years following this, the seasonal influence on serum calcium levels in patients with sarcoidosis led investigators to speculate on sunlight's influence and vitamin D consumption [147]. Adams, in 1983, suggested that alveolar macrophages synthesized 1,25-(OH)2-D3 in patients with sarcoidosis, showing that the hormone is produced outside of the kidney [148]. In a large series from Italy, Rizzato and colleagues noted that in 618 cases of sarcoidosis, calculi were the presenting symptom in 1 % [149]. Stones have been noted to occur in about 10 % of these individuals. Hypercalciuria represents a primary risk for stone formation [150]. Hypercalciuria is three times more common in sarcoidosis patients than is hypercalcemia. Current mechanisms proposed for this phenomenon include absorptive secondary to 1,25-(OH)2-D3 on the bowel, resorptive with sarcoid involvement of the bones with resulting osteopenia, and finally osteoclast-activating factor perhaps produced by activated inflammatory cells (lymphocytes and monocytes) causing further bone resorption [151].

Vitamin D has been known as a fat soluble "factor" found in the diet since sought by Sir Edward Mellanby in 1919. Rickets was a recognizable clinical problem at the outset of the eighteenth century. Ergosterol or vitamin D2 was identified in the 1930s initially in plants, and Windaus discovered vitamin D3 in the skin of animals in 1936. It seems appropriate to discuss the clinical entity of vitamin D intoxication following sarcoidosis since the two clinical pictures are similar. Vitamin D intoxication and sarcoidosis have, in fact, been likened to the same clinical findings in patients with absorptive hypercalciuria, type I [152]. In health, serum 1,25-(OH)2-D concentrations average about 85 pmol/L. Variations in dietary calcium across the usual normal range do not normally appear to alter 1,25-(OH)2-D levels. Parathyroid hormone augments renal production as does dietary phosphate [153]. Sunlight exposure, particularly high-energy photons from the ultraviolet B (UVB) wavelengths between 295 and 305 nm, is responsible for vitamin D synthesis in human skin. Most people rely upon the cutaneous synthesis of vitamin D as the principal source of this hormone. Substantial amounts of vitamin D are present in fish and animal liver, egg yolks, and fish oils. The USA has had a long-standing policy of fortifying milk with vitamin D2 and D3 supplements. In other countries, breads, cereals, and margarine might also contain vitamin D additives [154]. A particular concern with this process in the USA has been outbreaks of vitamin D intoxication calling to question the methods used to evaluate the level of vitamin D in both infant formula and milk [155]. 13 brands of milk and 5 brands of infant formula purchased at random from local supermarkets in five eastern states were investigated, and high-performance liquid chromatography was used to measure vitamin D. Seven out of the ten samples of infant formula contained 200 % more of vitamin D than stated on the label. The highest concentration contained 419 % more than the label [156].

Vitamin D intoxication is a well known but increasingly rare clinical condition probably secondary to the use of histamine-2 blockers for the treatment of indigestion and gastric peptic disease. Patients exposed to excess vitamin D consumption have hypercalcemia and occasionally metastatic calcification secondary to mobilization of skeletal calcium. In addition, patients suffering from this malady also can have significant hypercalciuria, stone formation, nephrocalcinosis, and occasionally acute renal failure [157]. The incidence of this disease has been declining, but the outbreaks have been reported with continued regularity. In one long-term crossover trial of the vitamins D in 6 patients with hypoparathyroidism, the relative potencies were as follows (assigning vitamin D an arbitrary potency of 1): vitamin D2 1, dihydrotachysterol (DHT) 3, calcifediol 10, alfacalcidol 750, and calcitriol 1500. This study points out the twofold superiority of calcitriol over alfacalcidol. In addition, an important subgroup of patients who are managed with vitamin D therapy is at risk for the development of vitamin D toxicity, namely, those patients that have iatrogenic hypoparathyroidism. Several series of such patients indicate the significant potential risk of being overtreated with either alfacalcidol or calcitriol and secondary development of toxicity. Several of these series have patients presenting with stone disease [158–160].

Modern Synthesis

So the history of urolithiasis is now mostly up-to-date with this chapter, and the final curtain rises and it is time to present our most current knowledge. Have we found the elusive cause of urolithiasis, or as Randall himself stated, "*When one undertakes to explain the origin of stone in the upper urinary tract, one appears to be confronted by the fact that our theories of today seem to be increasing the complications of the picture rather than its simplification*" [129]. Randall's notion of his two lesions arising in the papilla of human kidneys floundered for a while, never truly gaining in scientific circles because so much work was being done in basic stone chemistry, physical chemistry, and crystal-cell interaction work [161]. The old notion in progress, two steps forward and one step back applied [162]. But the evidence was on the wall, so to say, an elegant progression of fixed particle theory had not been disproven, simply displaced [163]. By the mid-1980s and the 1990s, the tide was about to turn on Randall's hypothesis once again, and new methods of examining papillary pathology would begin to have profound influence on basic science of stone formation again [164–166]. Low begins "*Papillary 'Randall's plaques' are theorized to act as nidi for urinary stone formation. The aim of this study was to document the presence, pattern of distribution of Randall's plaques in patients undergoing endoscopic procedures for urinary stone disease*" [166]. The floodgates were reopened, and the scientific scrutiny of Randall's long-held notions of two primordial lesions would now begin in earnest.

The best data would of course come from live human stone patients, and the ability to biopsy the papillary lesions associated with stone formation became available with the advent of modern endourologic techniques. Beyond just simply mapping human papillary pathology, very carefully performed anatomical, histological, spectroscopic, and electron microscopic scrutiny of living human tissues was carefully begun at the Methodist Hospital in Indianapolis bringing researchers from the University of Chicago for correlation with urinary chemistry abnormalities to generate an overall model of all types of stone-forming pathology. We have already discussed international stone meetings, but have left one out, that is, the Annual International Urolithiasis Research Symposium in Indianapolis. At the inaugural meeting held from November 2–3, 2006, many of the researchers interested in developing an overall model to explain stone development presented their work [167]. Let's use Fred Coe's summarization of the opening talk to highlight this synthesis:

Table 29.6 Summary of the synthesis of the modern model of stone formation (ala Fred Coe)

Phenotype	Stones	Interstitium	IMCD BD
ICSF	CaOx	Heavy plaque	Nothing
Obesity bypass	CaOx	No plaque	Apatite plug
CaP SF	Brushite	Plaque	Apatite plug
	Apatite	Plaque	Apatite plug
dRTA	Apatite	Normal plaque	Apatite plug
Cystinuria	Cystine	Normal plaque	Apatite & cystine plugs

"*I would like to summarize the findings from the human biopsies in a more compact form showing the phenotype, the type of stones, what is forming in the IMCD [inner medullary collecting ducts] and ducts of Bellini (Table 29.6). ICSF [idiopathic calcium stone formers] have CaOx stones, of course, heavy plaque and nothing in the epithelial compartment. Obesity bypass patients form CaOx stones; they have no plaque (i.e. below what one finds in normal people) and apatite plugging in IMCD. Calcium phosphate stone formers with brushite stones have plaque above normal and apatite plugging of IMCD and ducts of Bellini. Apatite stone formers have plaque in modest abundance above normal and apatite plugging. Distal renal tubular acidosis (dRTA) patients form apatite stones; they have no more plaque than that of normal people and have apatite plugging. Patients with cystinuria form cystine stones; they have normal amounts of plaque (i.e. as normals) and they have apatite and cystine plugs in the IMCD and ducts of Bellini*" [167].

A more succinct and specific summary of large volumes of research information does not portray the events of stone formation any better than this relatively short paragraph. All of the crystal-cell interactions are gone, intracellular processes are removed, the genetics are not considered, but the simple observations of real human patients and an underlying process are documented, revealing what are probably common final pathways leading to symptomatic stone formation. Alexander Randall's two fundamental observations are taken to the next level. I would like to complete this modern synthesis from another epicenter for basic stone research, the Mayo Clinic, and summarize the cell biology of pathologic renal calcification [168]. This paper summarizes large volumes of basic cell research and succinctly presents the overall state-of-the-art picture, taking us from Fred's elegant model to the conditions leading to these observations. The very earliest crystalline deposits arise near the thin limbs of the loop of Henle and in the basement membrane surrounding the vasa recta [169]. The Mayo group shows that polyanionic molecules may act defensively and that dysfunctional macromolecules (such as Tamm-Horsfall protein or THP) perhaps secondary to decreased sialic acid content might contribute to CaOx and CaP crystals adhering to collecting duct cells [168]: "*Adhesion of CaOx crystals from nephron fluid to renal cells may be particularly important in states of marked hyperoxaluria, such as primary or enteric hyperoxaluria*" as presented above by Coe [168]. Next, they present compelling data that crystals can arise directly in the interstitium as the renal cells can behave like osteoblasts, expressing bone-associated proteins osteopontin and bone sialoprotein to form calcified nodules thus promoting Randall's plaque buildup. Finally and perhaps the most radical notion they present is the possibility that a primitive infectious particle nanobacteria might also be involved. They present compelling data to support this hypothesis: "*Although it is assumed that the unique ionic milieu in the medulla near the loop of Henle promotes the growth of these calcium phosphate deposits via physicochemical mechanisms, is it possible that this same milieu may be ideal for the growth of nanoparticles and that perhaps they preferentially colonize here*" [168]. This is enough for us to ponder in this historical discussion of the modern science of stone disease with the exception of genetics.

Stone Genetics

"*In biological phenomena differences from the mean follow the same laws as differences in the mean in all other kinds of phenomena controlled only by chance.*"

—Hugo de Vries, 1909

Genetics did not really begin with the Austrian monk Gregor Mendel nor did it die with his death in 1884. But a quantum leap occurred on the evening of February 11, 1865, with an audience of about forty people in the Realschule in Brno when he gave his first communication of his monumental work on hybridization of peas [170]. The cell had become the "*seat of life*" according to Virchow, and Haeckel had noted that the "*internal cellular nucleus and external cellular substance are the only two essential parts of every real cell. All the rest is secondary and accessory*" [171]. Staining of the nucleus revealed "*chromitin*" which was used by Walther Flemming in 1902, and Weldeyer called the filaments "*chromosomes*" [172]. Sutton documented the significance of chromosomes in genetics with his 1903 paper *The Chromosomes in Heredity* [173]. The first international congress on genetics was held in London in 1906. William Bateson, a botanist, used the word genetics that was derived from "genesis" for the new science [174]. Archibald Garrod became one of the first to report a genetic disease, alkaptonuria, which he traced in 1902 and wrote that it was inherited as a "*Mendelian recessive*" [175]. James Watson and Francis Crick unlocked the basic structure of deoxyribonucleic acid in 1953, perhaps the climax of the genetics introduced by Mendel [176, 177]. The Human Genome Project was conceived by Robert Sinsheimer at the University of California at Santa Cruz and Charles DeLisi the director of the Office of Health and Environment of the US Federal Department of Energy in the mid-1980s. Sinsheimer held a meeting in 1985 on the Human Genome Project at Santa Cruz, and DeLisi followed this with one at Los Alamos in 1986 with the GenBank, a major database serving as the repository of data. The National Institute of Health decided upon major funding of this project and named James Watson as director of research in 1988. The European organization was founded in the same year, Human Genome Organizations or HUGO. Real-time funding and advanced research began in earnest in October of 1990, and it was estimated that it would take decades to complete the task of discovering the estimated 20,000 to 25,000 human genes (3 billion DNA subunits), but improvements in technology resulted in a completed genome by 2003. There have been 1,800 disease genes isolated, there are more than 2,000 genetic tests that can be performed, and an estimated 350 biotechnology-based products have emerged from this genetic research [178].

It has long been known that about ½ of patients who develop a calcium oxalate stone and are found to have hypercalciuria have a positive family history of nephrolithiasis [179]. Though originally thought that hypercalciuria might be an autosomal dominant condition, this is now known to be a complex trait that does not follow simple Mendelian inheritance [180]. There are monogenic diseases that lead to hypercalciuria, and these are listed in Table 29.7 [181]. The monogenic causes of hypercalciuria are more heterogeneous than those listed in the table, but they allow great insight into the generic alterations that cascade through transcription to gene products that ultimately cause disease (phenotype). There are now plenty of animal knockout models as well, and all of this information might be leading to new strategies for therapy. In addition, the growing number of mouse knockout single-gene deletions provides a valuable data set for genes that can be screened in human diseases. Associated gene linkages can be studied such as vitamin D-receptor alterations and osteopontin or Tamm-Horsfall protein changes [180]. A stunning array of basic genetic research is on the horizon, and both the rat and the mouse genome have been fully recorded for researchers [182].

In closing a historical sketch about genetic foundations of urolithiasis, it is interesting to find an absolutely fascinating account of a twin study on stone disease. Goldfarb and colleagues provide such a fitting end to this section [183]. The issues surrounding stone formation and lifestyle are ideally suited for twin studies, nature versus nurture. This registry included dizygotic twins with 17 concordant pairs and 162 discordant pairs for kidney stones. It also included monozygotic twins with 39 concordant pairs and 163 discordant pairs. These subjects were analyzed for complex heritability risk for stones, which was 56 % (more likely than not). Protective dose-response patterns in these twins included coffee drinking (more than five cups daily was

Table 29.7 Known genetic causes of stone disease (modified from Coe et al.)

Disease	OMIM	Inheritance	Locus/gene	Phenotype
Monogenic hypercalciurias				
Dent disease complex	300009, 310468, 300008	X-linked	Xp11.22/CLCN5	Hypercalciuria, phosphaturia, proteinuria, CRF, rickets
Bartter syndrome type I	601678 600359	Autosomal recessive	15q15-21/SLC12A1	Hypokalemic alk. Na wasting, Hypercalciuria
Bartter syndrome type II	241200 600359	Autosomal recessive	11q24-25/KCNJ1	Hypokalemic alk. Na wasting, Hypercalciuria
Bartter syndrome type III	607364 602023	Autosomal recessive	1p36/CLCNKB	Hypokalemic alk. Hypercalciuria
Bartter syndrome type V	601199	Autosomal dominant	3q13.3-q21/CASR	Hypokalemic alk. hypomagnesemia, Hypercalciuria, CRF
Autosomal dominant hypocalcemic hypercalciuria	146200 601199	Autosomal dominant	3q13.3-q21/CASR	Hypercalciuria CRF, hypocalcemia, hyperphosphatemia, low PTH, tetany
Familial hypomagnesemia, hypercalciuria, nephrotic syndrome	248250 603959	Autosomal recessive	3q27/PCLN1 (CLDN16)	Hypercalciuria, hypermagnesuria, polyuria, dRTA, CRF, low mag, tetany, seizures
Primary hyperoxalurias				
PH type I	25990 604285		2q36-q37/AGXT	Hyperoxaluria, CRF hyperglycolaturia
PH type II	260000 604296		9cen/GRHPR	Hyperoxaluria, CRF L-glyceric acid excr.
Distal renal tubular acidosis				
Autosomal dominant dRTA	179800 109270	Autosomal dominant	17q21-q22/SLC4A1	Osteomalacia, hypokalemia
Autosomal recessive dRTA with hearing loss	267300 192132	Autosomal recessive	2p13/ATP6V1B1	Hearing loss, growth failure, rickets, hypokalemia
Autosomal recessive dRTA	602722 605239	Autosomal recessive	7q33-34/ATPVOA4	Growth failure, rickets, hypokalemia
Cystinuria				
Cystinuria type A (type I)	104614	Autosomal recessive	2p16.3/SLC3A1	Heterozyg: nl. cystine Excretion
Cystinuria type B (type non-I)	604144	Incomplete autosomal recessive	19q13.1/SLC7A9	Heterozyg: elevat. cystine excretion

protective), drinking at least one cup of milk daily was protective, and marginally protective effects from tea, fruits, and vegetables were noted. The typical deleterious dietary factors usually listed such as calcium supplements, alcohol, and animal protein were not noted to be significant. One comes away from this study wanting more data comparison because of the power of controlling for the genome among twins.

Discussion

> *"The universe as we know it is a joint product of the observer and the observed."* [184]
>
> —Pierre Teilhard de Chardin

We do have a ways to go before our final understanding of urolithiasis is complete, when this scourge upon mankind will finally be lifted from the suffering humanity. Our hope for a new dawn of epistemological progress perhaps will be complete with genetic therapies or some complex nutritional additive that will prevent the manifestations of urinary stone formation. In all of its complexities, urolithiasis is much like the ancient Roman notion so well recalled by van Beverwijck "*like becoming living statues*" [185]. He hypothesizes that the problem of stone formation is something in the urine itself. He does this rather artfully by quoting an absolutely delightful poem from Ovid:

"*Through the country of the Cicons*
Flows a stream that is most strange:
He who drinks it, pays most dearly,
As it will not spare the life
Of a thirsty creature drinking,
Where no thirst is ever quenched.
For, alas! What fearful ailing
Waits him: bowels turned to stone!
All that's floating in this river
Or but moistened with its water
Is at once seen stark and stiffening,
Till it is as hard as marble." [185]

The Malpighian tubules of insects are the forerunners of the development of kidneys, and one simply has to look to our understanding of the more simple renal prodromal units to have a built-in model of handling of complex crystalline interactions. Insects might just fit the bill for this model with a wide variety of species to choose. The silkworm (*Bombyx mori*), for instance, represents an ideal specimen because it has been extensively investigated because of their economic worth. One recently reported research effort looked at calcium oxalate crystal and macromolecule interactions; others have looked at dietary effects upon the calcium oxalate accumulation and the effects of inhibitors such as citrate [186]. The fruit fly (Drosophila melanogaster) has been one of the prime genetic models, introduced by Thomas Hunt Morgan (1866–1945) who pioneered so much of modern genetics. But the rapidly proliferative laboratory insect has proven a fruitful model for all types of urolithiasis research [187]. The note "*The addition of an insect model for elucidating the pathophysiology underlying stone disease and potentially developing new therapeutic approaches expands the repertoire of model systems, which have been primarily mouse and rat systems. There are advantages of the Drosophila system that should be noted, namely, (1) colonies, (2) the rapid deployment of new transgenic lines, (3) the ability to test hypotheses in lower-species* in vivo *systems before embarking on studies in more cumbersome higher-order animals*." One can only hope that the most abundant order of insects might become a urolithiasis model, the Coleoptera, because historically it was Charles Darwin's favorite [188].

Barnacles (Cirripedia) are arthropods that compete with limpets that are gastropods in many similar ecologic niches. Charles Darwin spent a considerable amount of his precious research time while pondering the origin of species studying minutely the subtle nuances of the barnacle. It was he who split the life cycle of the barnacle into two distinct phases: free-swimming larvae and the sessile adult [189]. He also described the cement gland of the barnacle and presumed it might be derived from the Malpighian tubules of this arthropod group [190]. The pair of kidney-shaped cement glands of Cypris larvae which do not feed are found ventrolaterally and that these glands create, store, and secrete the cement that is important for the sessile second stage of their life cycles. It is these glands that transport the cement via a cement duct onto the surface of the antennule attachment disc. The cement in these glands are stored in secretory granules which are 2–4 μm in diameter [190]. Limpets or Patellogastropoda also have complex calcium-producing cells that are necessary for forming attachments and their protective shells. There is intriguing work being done on these animal species as well [191].

The alpha and the omega—the beginning and the end—are mystical or metaphysical notions largely exploited by most religions but with parallels in life and disease.

As we have highlighted the rising prevalence of stone disease in all aspects of our modern populations, it might be worthwhile to point out that nephrolithiasis in children is also on the rise. Though childhood stone disease represents a less well-known population than in adults, there is compelling evidence that our children are getting kidney stones with increased prevalence as well, perhaps dramatically so. The Hopkins group recently looked into a nationwide database called the Kids' Inpatient Database (KID) which includes discharges from 22 states in 1997, 2000, and 2003 [192]. They also calculated that the rate of increase was 365 % in females and 274 % for males during this period of investigation. It increased across all juvenile age groups 0–5, 6–10, 11–15, and 15–20. They concluded that "*Furthermore, the incidence of treated stone disease appears to be increasing at a great rate in the pediatric population. Further studies should build on this hypothesis-generating work and define the effects of metabolic and environmental risk factors that may influence stone risk in the pediatric patient population*" [192]. And as if in response, there has developed a directed risk factor analysis with sibling controls looking into this burgeoning problem. In a pediatric population of 129 stone-forming children compared to 105 non-stone-forming siblings and 183 normal, healthy controls all aged from 6 to 17, urinary chemistries were performed [193]. They discovered that the spectrum of abnormal findings was remarkably similar to that found in adults with the principal risk factor being hypercalciuria: "*Stone formers have strikingly higher calcium excretion along with high supersaturation for calcium oxalate and calcium phosphate, and a reduced distance between the upper limit of metastability and supersaturation for calcium phosphate, indicating increased risk of calcium phosphate crystallization. Other differences in urine chemistry that exist between adult stone formers and normal individuals such as hyperoxaluria, hypocitraturia, abnormal urine pH and low urine volume were not found in these children. Hence, hypercalciuria and a reduction in the gap between calcium phosphate upper limit of metastability and supersaturation are crucial determinants of stone risk. This highlights the importance of managing hypercalciuria in children with stones*" [193].

At the other extreme, we are at a unique point in human history when the population growth rate in the aged will be larger than the younger. Elderly patients have many geriatric issues that other stone-forming patients do not, such as already significant skeletal bone mineral loss, previous fractures, immobility, a host of medications, and mineral supplementation. Vitamin D deficiency increases with age and supplementation in this age group is common [194]. They at least mention a cautionary caveat about being careful in stone-forming elderly patients. Don Gentle looked at 721 geriatric patients who were stone formers and noted that in general, their first stone event was after age fifty. Two thirds of these elderly had abnormal urinary chemistries and 29 % were hypercalciuric. He also noted that the severity of disease was equivalent between the geriatric group and the normal stone group with the exception that geriatric parathyroid disease was more common. Finally, as one might expect, uric acid stone disease increases in the geriatric population [195]. A Japanese study also looked at 209 elderly stone formers over age 65 who consisted of 9.6 % of their stone population. Calcium-containing stones made up 80 % of this group though they too noted that uric acid stone formation was higher, in 10.7 % (vs. 5.1 % in younger stone group). Stones recurred in 154 % of these elderly patients, so the same treatment applied [196]. One final paper from Russia looked at elderly patients to see how they fared after surgical interventions. Like the younger cohorts, the treatment of symptomatic stones greatly improved the quality of life of both presenile and senile patients with stones [197].

Our science has come a long way, and there are those who are pessimistic and believe the research will go on forever before any meaningful strides have been made towards conquering this disease. There was also Alexander Randall who steadfastly to the end maintained that there was no such thing as "kidney stone disease." The nanoparticles that have enthralled Lieske at the Mayo clinic have also fascinated David S. McKay who is a NASA scientist famous for suggesting that Martian Meteorite ALH84001 also contained these nanobacteria. ALH84001 arrived on Earth about 13,000 years ago, and it was ejected from Mars about 4.5 million years ago [198]. It would be extremely ironic if life was seeded upon Earth by such biologic impacts in the early formation of this planet, and irony would be hardly the point if that primitive life was stone forming itself.

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30 Equal Rights: Stone Disease and Females

Introduction

> "*Prejudice is so powerful that, even without Reason, reputations are established. In order to avoid this rock in describing Causes, Symptoms and Remedies of Stone and Gravel we will weigh anchor for the open sea of Experience*." [1]
>
> —Johan van Beverwijck (1641)

The oldest known stone sufferer currently is a woman about 8,500 years ago. She was a Mesolithic cave dweller who had a predominately calcium-containing bladder stone. We do not know much about the earliest humans, but our knowledge has expanded significantly in the past century or so [2]. In 1863 the Anthropological Society of London was set up including the members Sir James Hunt, Richard Burton, and Robert Knox the anatomist. Knox was a gifted anatomist and teacher in Edinburgh but became involved with William Hare and James Burke who were not above helping unfortunate people into early mortality. In November 1827 Hare was paid £7.10 (seven pounds and ten shillings) when an indebted lodger died on him and he delivered the body to Knox. Hare induced his partner James Burke into 16 more "transactions," in what became known as the West Port Murders. On November 2, 1828, Burke and Hare were caught, and the whole city was in an uproar, fed by poems and scandalous newspaper accounts about the terrible deeds of Burke and Hare. Hare turned on his colleague, and Burke was hanged, dissected (the most appropriate punishment for murder for a resurrectionist), and displayed at the Royal College of Surgeons of Edinburgh (I've personally seen his remains). Knox fled to London and wrote on early anthropologic theory [3]:

> "*Burke's the butcher, Hare's the thief,*
> *Knox, the boy who buys the beef!*"

The Egyptians apparently had no qualms about gender and delivery of medicine. The first known woman physician was Peseshet and is immortalized on the Stele's hieroglyphics (3100–2100 BCE). Another woman physician was Merit Ptah, also about 5,000 years ago, who was known as the "*chief physician*." We also know that the Egyptians specialized in every illness according to Herodotus. It is possible that a woman was a stone specialist even at the earliest times. This rather liberal view of gender accomplishment would not last beyond the Golden Age of Egypt; however, with the rise of Persian Empire and the subsequent Greek conquests of Alexander the Great, the female physicians and health care would be arrested, at least from public scrutiny though probably not in reality, for the midwives would fill the void of the male physicians and quite probably treated women with stone disease [4]. Alexander brought his own physician with him, and it is probable that the Indian methods of lithotomy were influenced by Greek physicians [5].

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Women of Greece

In ancient Greece, life for women was limited in many ways compared to women in modern America. For instance, ancient Greek women had few legal rights; they had no control over marriage, and could not participate in government. The women of classical Greece were forced to adapt to their restricted role in a male-dominated society and developed interesting ways to overcome their limited role in society. One particularly interesting method is illustrated by the ways women became involved in the health care of the ancient Greece. Women in the ancient Greek world were controlled either by their fathers or by their husbands, depending upon what point in their lives was viewed. They owned nothing and had the most restricted rights. The work and freedom that women could achieve depended on their social status in the society [6]. There were the poor, the slaves, the wives, and the Hetaerae who were prostitutes with more education [6]. No matter what class they were in, whether it be through marriage or birth, women were still considered "lower" than men. From birth, girls were not expected to be given a formal education. Reading and writing were thought to only be appreciated by men and the Hetaerae [7]. Women were expected to learn the ways of motherhood and the chores of the household, an entirely different type of education than what men received [7].

The social status of women in ancient Greece is apparent from the laws that began to identify women's rights. Dakron first identified women as a particular aspect of the state's responsibility [6]. Solon went even further in defining a woman's place in the Athenian society [6]. The Democratic Constitution identified women as citizens with rights and obligations. Pericles further clarified the role of women as citizens [8]. Finally, Xenophon's *Oeconomicus* gives a modern glimpse into the daily lives of women in Athens [8]. Nowhere is it mentioned what women could be allowed to do outside of the house, yet there is compelling evidence that women were vital in taking care of injured soldiers, serving as nurses, and helping other women with female health issues, especially with childbirth perhaps even those suffering from stones [6].

The most documented influence was with religious ceremonies and worship where female goddesses played a significant role in the minds of the ancient Greeks [6–8].

In Greek mythology, Pandora is the first female who is given to mankind by Zeus with the box containing all manners of human suffering [9]: "*Pandora, the bitch-mind and the womb-jar. She, as symbol of female difference, makes gynecology necessary to the Hippocratic enterprise*" [9]. Athena, the goddess of Athens is given the gift of knowledge and strength and is worshipped by Athenians for intervention during some illnesses [4]. Hera, the wife of Zeus, is likewise a sought-after goddess during illness. But the rise of the cult of Aesculapius on some of the islands in the Greek civilization resulted in the profession of medicine that prospered on Cos, an island now off the coast of Turkey [10]. Aesculapius had two daughters, Hygeia and Panacea, who are often depicted in scenes near the medical facilities of the times [10]. Hygeia becomes the name for the most effective methods for maintaining health, hygiene, and Panacea becomes the name for cures of all types, panaceas. Women were always pictured in the delivery of health care [10].

The first true indication that women played physically active roles in the delivery of health care in ancient Greece was in managing women's health problems, particularly gynecology although possible bladder stone disease as well [11]. In religious rights, menstrual blood was considered as a sacrificial offering, the symbol of fertility. The woman's role in fertility and the health of her body became significant interests of women practitioners, called midwives [11]. Contraception and birth control were issues discussed freely and even favored by great Greek philosophers such as Plato and Aristotle [12]. The Hippocratic physicians did not look favorably upon abortion, but it was practiced mostly by women midwives [11].

The Hippocratic physicians believed in the doctrine written down in the *Oath of Hippocrates* [13]. Women were not mentioned, but the practice of abortion was specifically mentioned as an admonition to avoid [10]. The doctor according to the Hippocratic view was a male, who guided the delivery and care of his patients. *Iatros* is the Greek word for the physician's role in the care of the sick [10]. This is the first formalized professional ethics that was written about how the doctor is expected to behave and care for those who are sick. No role is given to women, but they are not forbidden either [10]. Women clearly participated in ancient Greek health care, but played limited roles at the Aescalapian shrines and in specific roles in their own care during pregnancy, contraception, abortion, and menstrual or menopause troubles [12].

Women who wish to add more to their role in society than just a custodian of the home had little opportunity in ancient Greece. But there is good evidence that, though perceived at odds in this man's world, they did manage to slowly and steadily increase their influence in their society. The classic Greek comedy *Lysistrata*, written by Aristophanes and first performed in 411 BC, clearly showed women during this time being frustrated with their limited roles in society [14]. Lysistrata is the heroine who comes up with the daring plan to stop the wars and return order to the Greek civilization. She showed forethought, cunning, and the ability to organize and direct the women from all over the Greek city-states [12]. She took on an active role for a woman and in standing up for her ideals, demonstrated that people at that time were in fact aware that women could have something significant to offer [12]. She is a hero, not a villain, and her efforts were appreciated eventually by both the men and women of Greece. The women who struggled in relative obscurity acting as nurses, midwives, or assistants did their share and helped provide assistance to the sick of this era [11]. They too contributed to the society and eventually began to give women a more formalized acceptance into professions such as medicine [12].

Despite being forced into a stereotyped role in their society, women did manage to become integrated into all aspects of their society, including the rigidly controlled medical profession. Women in ancient Greece were not the topic of too many primary references in medicine, nor are they written of in nearly any role in society that we now take for granted such as physician, judge, lawyer, or architect. But, there is good evidence to suggest that women did in fact participate in health care and increased their abilities to add to their society [11]. It was medicine in particular that allowed these pioneering women some degree of integration in health care that just now is beginning to achieve equality [8]. We will leave the Greco-Romans after mentioning one of the main remaining sources on early lithotomy, Aulus Cornelius Celsus (c.25 BCE–c.50 CE) whose *De Medicina* is a treasure trove of ancient medical wisdom [15]. He comments on a woman suffering from bladder stones advising the extraction by using a transurethral hook, aided by a finger in the vagina. He also described incising the urethra under the pubic bone for larger stones. Let's quote from Celsus on catheterizing a woman and making the diagnosis of stones: "*The woman has a urethra both shorter and straighter-like a nipple placed between the inner labia over the vagina- which need aid no less often, but causes somewhat less difficulty*" (505) [15].

Female Anatomy Lessons

Crone-ology was the term first utilized by the feminist Mary Daly [16]. She was illustrating the point that women's legacies are difficult to piece together from the early part of mankind's history because of male-dominated educational and literature practices, and this applies to stone disease in the female population as well [17]. In point of fact, women have had a relatively lively past association with science in general and medicine in particular. We've just discussed the early Egyptian writings and pictures that demonstrated female involvement with medicine [18]. The Western tradition from ancient Greece continued this association with documentation from Homeric writings where women served as physicians and surgeons during the Trojan wars [19]. During the rise of Rome, many famous women physicians were prized in Roman society. Galen recounts specifically the skills of famous female physicians such as Agamede, Cleopatra, and

Philistra [20, 21]. The Cleopatra to whom he was referring was not the queen who gave to Caesar some of the Library's Treasures among other things. Cleopatra was a scholarly woman, possibly a physician in Alexandria who was contemporaneous to Galen, and her treatises on anatomy are now lost but referenced in other writings.

The fall of Rome led to the Dark Ages and the rise of intellectualism via the Roman Catholic Church which of course was/is a male-dominated fraternity. For Europe in general this period has been called a time of mental paralysis, a loss of written works and a decline in medicine in general. Lithotomy was still practiced as we have noted, but data on the incidence of stone disease simply does not exist. The Medical School of Salerno was founded in the early tenth century according to legend by a Jew, an Arab, a Greek, and a local native. The Salerno School thrived, and by 1140, they had requirements of 3 years of advanced education, 4 years of medical school and anatomy requirements for surgeons, and an additional year of practical training [22]. It is believed that one female professor, Trotula by name, was writing about anatomy and even stone disease in the eleventh century. We know little about this enigmatic woman and there is speculation that she married another professor, John Platerius I, and she had two sons who both became physicians [23]. We know that she was interested in anatomy and preventative medicine. She most likely authored the work *De Passionibus Mulierum Curandarum* (The Diseases of Women) often referred to as *Trotula major*. She probably wrote *Summula Secundum Trotulum* (Trotula minor) [24]. Her writings on women and female diseases is our third historical inclination that females did suffer from stones and the females were probably their source of health-care provision [25]. For difficulties in voiding which could be caused by stones for both men and women, she prescribed a bath of benedictum simplican and plaster of cooked watercress applied to the suprapubic region. For women, she added a fumigant of mint, laurel, pennyroyal, absinth, and mugwort. For stones of any type, she suggested sassafras and root of grass taken twice daily. If the stone became impacted, she recommended cooked mallow, sassafras, cabbage, Paritaria, watercress, ameos, nettle seed in wine, oil, and salt water applied to affected parts [26].

We can get some insight into the underground nature of stone disease in females by the writings of the Middle Eastern physician and author Abū 'L Qāsim az-Zahrāwī Khalaf ibn 'Abbās aka Albucasis who was born in az-Zahrā (c.936-1010/1013). His *The Practice and Method* book 30 dealt with surgery and lithotomy [15]. It is illustrated showing over 200 instruments and gives precepts derived from practical experience. He also gives instructions to midwives who dealt with stone disease in female patients in the Middle Ages [15]. Hildegard of Bingen (1098–1179) was a religious nun who also wrote extensively on medicinal herbology during the Dark Ages. She was the tenth child of her parents and was promised to the Church as a tithe at an early age. She became a German Benedictine abbess, author, perhaps physician, and in some ways a feminist which we will return to a bit later. Hildegard probably wrote her two treatises on medicine and natural history, known in English as *Book of Simple Medicine* and *Book of Composed Medicine*, between 1151 and 1161. She did mention stone disease and herbs that were successful at soothing the urinary tract [27].

The beginning of the Renaissance was associated with the rise of the universities in Bologna, Padua, Marseilles, and Paris, but the Salerno School with its gender neutrality was relegated to the past yet again. Female disease was once again given into the capable hands of the midwives. Laura Bassi did become the first professor at the University of Bologna in 1732 at the age of 21. She was interested in the electrophysiology that had begun with Galvani [28]. Next came Anna Morandi (1716–1774) who married Giovanni Manzolini who was an expert wax modeler. She had learned anatomy at Bologna and started making wax anatomical models and in 1755 was appointed as a lecturer in anatomy. Her talents were so remarkable that Pope Benedict XIV sponsored a public exhibition of her anatomical wax models still on display in Bologna (Fig. 30.1a). She did public anatomical demonstrations for Catherine the Great [29].

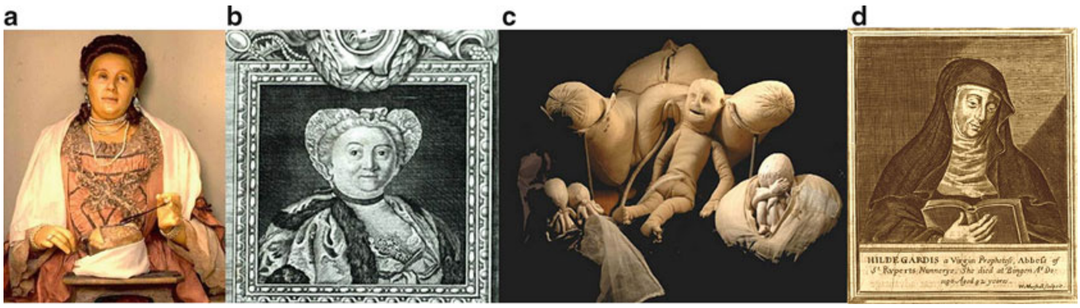

Fig. 30.1 (**a**) Anna Morandi (1716–1774) anatomist (wax model self portrait), (**b**) Angelique du Caudray (midwife extraordinaire), (**c**) du Coudray's birthing simulator, (**d**) Hildegard of Bingen

Now let our interest focus to the heart of enlightened France, heavily influenced by the philosophers Descartes and Spinoza, where independent thought had rekindled the notion that man (not woman, yet) could not only achieve what the ancient Greeks accomplished but perhaps even eclipse those immortals such as Plato, Aristotle, Hippocrates, and Galen. This was a France in the thralls of Voltaire's massive literary outpouring, purporting such notions as his character, Candide [30]. Surgeons were becoming ascendant in medicine, midwives were struggling to maintain their autonomy, and the average French person remained illiterate but increasingly aware of the world and ideas that abound. One woman had recently published the first scientific book on Newtonian physics in French, Emilie du Chatelet, who not surprisingly also happened to be Voltaire's mistress [31]. In addition, reproductive physiology and scientific investigations had recently sparked none other than William Harvey to present his mature life's work on generation. This in turn stimulated an altogether luminous period of investigative research from van Horne, Stensen, de Graaf, Swammerdam, Redi, and the amateur Leeuwenhoek into the actual mechanisms of reproduction [32]. Judith Drake (1696–1723) was the sister to Dr. James Drake famous for his anatomy text in London. Judith probably practiced medicine (as a midwife officially) but published one of the first treatises on women's rights. In addition, she probably wrote the section of her brother's textbook *Anthropologia Nova; or a New System of Anatomy* [33]. She read and wrote extensively on William Harvey's, Swammerdam's, and de Graaf's theories of fertilization and embryonic development. She is mentioned as having some sanctions made against her practicing on female patients in London, and she wrote a famous tract on the foolishness of male stereotypes of females [34]. Genevieve d'Arionville (1720–1805) wrote a treatise on medicine, anatomy, and physiology with her own illustrations. Maria Agnesi (1718–1799) became a professor of mathematics. Jane Sharp was another interesting practitioner of midwifery in the seventeenth century who wrote *The Midwive's Book* in 1671 [35]. There was also Maria dalle Donne (1778–1842) who was thought highly enough by Napoleon that he made her the chair of obstetrics in Paris [36].

Most people lived in larger cities, and the average woman was illiterate, profoundly superstitious, and passionately religious (Roman Catholic in France). The women had a strong sense of purpose, however related to the doctrine of "*the Great Chain of Being*," though almost assuredly incapable of discussing the implications [37]. This was the officially recognized hierarchical dogma espoused by the Church placing all in a non-malleable order: God, angels, king, man, woman, and dog (unless of course the dog is particularly intelligent or a good hunter). These peasant women were strong, hardy laborers, sensual housewives who took to their station in life with passion. These women most certainly formed stones; even though kidney stones were untreatable, they occasionally formed bladder stones. Europe had been torn apart by war, and France was reeling from the loss of its sons to this strife but facing prolonged conflicts now with England. Reproduction, especially the birth of strong, healthy sons had taken on a political fervor, especially in light of 200,000 babies who died annually in France. But we have no data on female stone disease; it is only the occasional stone-forming woman who creeps out of the darkness and into written records.

One very notable feminine figure needs to be discussed, Angélique Marguerite Le Boursier (1715–1794) (Fig. 30.1b). It is appropriate that she should figure so strongly in this presentation, because in our era of rapidly changing technology, loss of physician autonomy, time constraints of our educational systems, mandatory work week limits for our urologic house staff, the rise of surgical simulation and documentation of five basic proficiencies that this enigmatic woman has much to offer [38]. All of these factors contribute to our current infatuation with simulation in our urologic residency and postgraduate education programs [39]. Simulation is not a new concept, and the power of this modality to strongly influence people derives from another Latin-derived technology, the simulacra or "talking head." A simulation remains a powerful modality to represent an abstract concept, so to more readily learn or adapt to a new skill. Jacques de Vaucanson, Francois Quesnay, and Claude-Nicholas Le Cat (famous lithotomist) represent seventeenth-century proponents of simulators in medical education; they were most interested in surgical simulation especially for lithotomy, but there is no evidence that any of these three luminaries had any substantive success [40]. Both de Vaucanson and Le Cat were attempting to make wet simulators for teaching lithotomy. On the other hand, the obscure heroine of this tale had a profound effect that serves to remind those of us who teach and uphold the original tenets of the Hippocratic Oath, albeit ignoring admonitions against operating upon stone sufferers, as something that defines the medical profession [41].

In the pantheon of great female accomplishment in medicine and in science, Madame Le Boursier du Coudray should humbly be added with full homage due to one who had accomplished so much. She attracted the attention of powerful physician allies, especially Jean Baseilhac, known internationally as Frère Côme and a great lithotomist. In addition, she was noticed and encouraged by Morand (who befriended Cheselden and was doing research on stone disease) and later by Sües, two physicians who rose in royal appointment to become censors. She developed, manufactured, and utilized an advanced birthing simulator in the eighteenth century throughout France (Fig. 30.1c) [41]. She selflessly instructed all who presented themselves to her for instruction at no cost for nearly 30 years. She retired at age 70, leaving a legacy that has somehow managed to be lost until recent scholarly investigations have found her great contributions again [41]. That women had few options from the Middle Ages through Enlightenment makes du Coudray's accomplishments even more significant [42]. In the June 2005 issue of Prairie Schooner, a poem about "*Madame Du Coudray's Woman Machine, 1756*" in part reads:

> "*She listened while they spoke of prolapse,*
> *mangled parts, torn limbs and broken backs,*
> *the ragged, filthy fingernail of someone's*
> *helpful aunt or neighbor tearing sight*
> *from a child's eye. From these tales*
> *she fashioned her machine, pushing*
> *her needles through the flesh colored cloth*
> *as capably as she pushed her hands,*
> *mercifully clean, into the darkened rooms*
> *of a thousand unupholstered wombs*." [43]

We've now introduced two substantial Enlightenment lithotomists that perhaps had some influence on Madame du Coudray, but one of them deserve more careful attention. Claude-Nicolas Le Cat (1700–1768) was born in Picardy and studied anatomy and surgery in Paris. He was appointed surgeon to the Archbishop of Rouen in 1726 and eventually as head surgeon at the Hôtel Dieu in Rouen. He performed a large number of lithotomies and invented many of his own instruments. He was passionately interested in anatomy and strove to develop an anatomical simulator that he could train other to perform surgeries, such as lithotomy. In 1749 an English translation of his paper The Operation of Lithotomy on

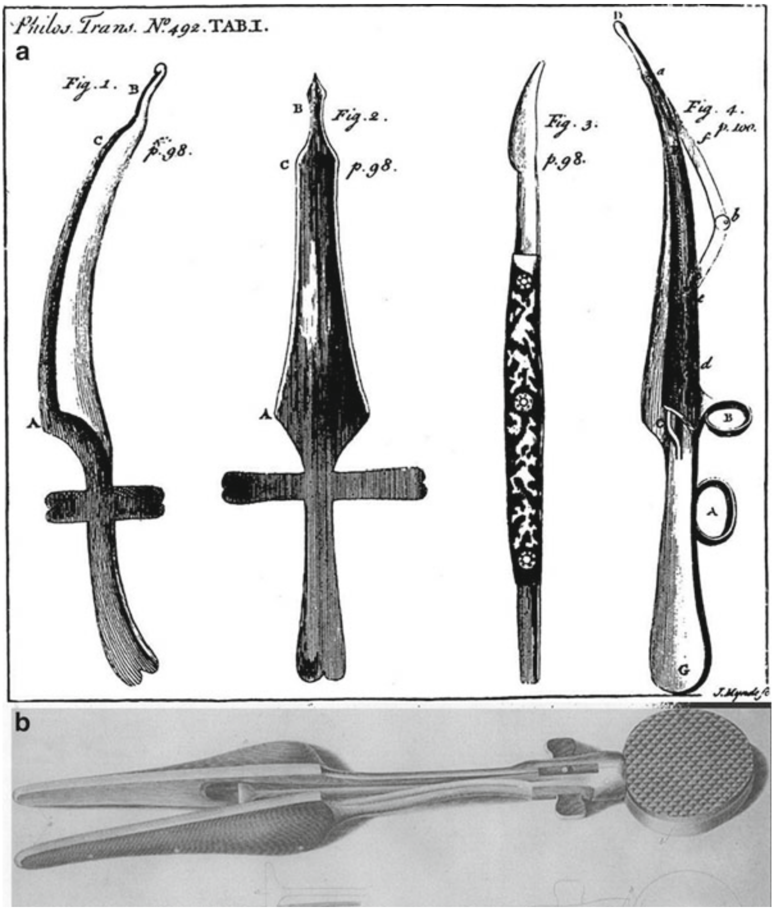

Fig. 30.2 (**a**) The female lithotomy instruments of Claude-Nicolas Le Cat, (**b**) the urethral dilation instrument of Sir Astley Cooper

Women was published in the Philosophical Transactions [44]. He begins with "*The lateral Way of cutting for the Stone, which I have used on Men since 1732, naturally led me, in the Year 1735, to cut the Widow Neel, a Farmer near Yvetot in the Pais de Caux in the same manner, as has been seen in the Observation*" [44]. He continues by describing his instruments in some detail, and following his first case, he further modifies his approach. He includes an illustration of his female modified instruments (Fig. 30.2a) He describes his second case "*…is Magdalen le Marchand of Pais de Caux, aged 22, cut in May 1738. I extracted a large Stone from her, and she was cured in ten Days*" [44]. He does not disclose how many female patients he operated upon, but he states he "*has succeeded perfectly well*" [44]. He concludes with a final case presentation, "*Mary le Comte of Diepdal near Rouen, aged 12, cut the 24th of May 1740, had a Stone of middling Size. In three Hours she retain'd her Urine, so as not to discharge it but involuntarily…There was not the least Suppuration. Mary le Comte perform'd all the Functions of this Organ, as usual; and being tired of the Bed, to which she was confined against her Will, she got up the third Day, in good Health, without any Accident supervening*" [44]. He has the illustration of his instruments and includes an explanation of their use "*that those who like it, may make use of it*" [44].

Stones and Gender Through Time

> "*He [Morand] informs us that it is much more frequent in males than females; and that almost all Rats, when they become old, have stones in their urinary passages, and swellings and ulcers in the kidneys*." [45]
>
> —W. Bingley (1809)

Modern statistics and the growth of information regarding diseases have interested throughout this entire book; it is in fact closely linked to the history of medicine itself. But women and female statistics are painfully lacking. This is no mistake and there are no errors. Much of our history is male dominated simply because the male dominated! There is a lack of data on feminine suffering simply because there were no successful female histories. Our written record, time and time again has been a record of victors, plain and simple. Now this is a history about stone disease so it should not at all surprise the reader then to note how little literature is available in our historical sources on this disease affecting the other ½ of our societies. We will endeavor now to piece together the precious few artifacts that are so minutely documented from previous historical sources.

Recall that we have already met with the famous stone of Trinity College, Cambridge. This was famously recounted by William Heberden who noted Mrs. Raisin's suffering and symptoms noting that surprisingly she suffered little. Again back to his account, "*…and might probably have liv'd much longer with it, if she had not thought herself well enough to attempt a Journey on Horseback; for, while she was riding, she was suddenly seized with violent Pains, that obliged her to be taken off the Horse immediately; After which she could never make Water, unless the Stone was first moved, and she continued in great Agonies till she died*" [46]. Let's begin with the opening of William Heberden's paper to the Royal Society on this stone in 1750: "*There is preserved in the Library of Trinity-College in Cambridge, a Stone taken from a human Bladder, which for its uncommon Size, may deserve the Notice of [t]his, Society. It is of an oval Shape, flatted on one Side and its Surface is smooth. The specific Gravity plainly shews, that danit is of an animal Origin; for its Weight is to that of Water only as 1,75 to 1*" [46]. Heberden takes some pains to produce a litany of eyewitnesses who can testify as to the true nature of this unusual case listing Right Rev. Dr. Claggett, Bishop of Exeter, the Rev. Dr. Baker, and the son-in-law of the patient who died with this stone. We have discussed the lithotomists in Norwich in some detail. One early name was a barber-surgeon named Gutteridge (or Goodrick) who lived and practiced for a time in Bury St. Edmunds before moving to Norfolk. His son apparently apprenticed with him and they came to notoriety for being asked to see Mrs. Raisin, but it appears they removed her stone only post mortem. No one appears to have treated the unfortunate Mrs. Raisin, and her stone history is again one of those exceptional quirks of fate that attracted the attention of the famous physician Heberden. The Norwich civic records certainly detail the community's presence of stones among the poor, mostly boys; there are no women recorded in these earliest of stone series [47].

The Norfolk and Norwich Hospital also kept detailed records on stone formers that were admitted to their institution from 1722 to 1909. Of the 1,498 stone cases that were admitted, only 53 were females [47]: "*The presence of only fifty-three female cases among 1,498 stone cases in the Norwich series illustrates the well-known sex difference in the incidence of bladder stone. This has been known since the time of Hippocrates who wrote that 'female children are less liable to stone because the urethra is short and wide and the urine passes easily…in males it is not straight and it is narrow as well*'" [47]. In the records from the Norwich School of Lithotomy, there are also some statistics which also shed some light on the treatment of female bladder stones. The hospital registers contain the records of 1,498 cases of bladder stones, of which all but ten autopsy specimens were removed by surgery. Table 2 of Shaw's article shows the age-adjusted trends of females in the Norwich Collections. There were 53 stones in women compared to 1,445 in males [47]. It is curious that the greatest numbers of female stones were also in the young with 34/53 (64 %) occurring in those under the age of 31 possibly indicating the same hypothesized etiology, endemic diets similar to those in third world countries today.

Another legacy of the Norwich School was the use of the vaginal lithotomy originally described by one of the founding fathers of the Norfolk and Norwich Hospital Benjamin Gooch (1708–1776). This operation was also used by Williams in 1882 for removal of a bladder stone from a woman aged 61 [48]. In addition, the lithotomists between 1772 and 1909 removed 35 bladder stones from females using a procedure called "*dilation and evacuation*" which involved dilating the urethra and extraction of the stones using forceps or finger. J. Yelloly described a particularly large bladder stone extracted in this fashion in 1815 [49]. Finally, the native son, Sir Astley Cooper would likewise utilize this technique for handling the few female bladder stones that he was asked to treat in London. In 1822 Cooper wrote about removing even large bladder stones by dilation of the female urethra with an innovative dilating device (Fig. 30.2b) [50].

The special committee of the Académie des Sciences that investigated the findings of Civiale regarding the superiority of his lithotripsy methods in 1835 also commented upon female stone disease: "*It has long been known that calculi are far less frequent among women than among men. In addition, among women, the chances of success after an operation are far greater. The numerical results obtained on this point tend to prove that over an equal number of operations, half as many women as men are lost*" [51]. Sadly they did not comment further on the incidence of stone disease in women any further than to decry the disease predominates in males.

Theories of Gender Superiority

> "*Women are told from their infancy, and taught by the example of their mothers, that a little knowledge of human weakness, justly termed cunning, softness of temper, outward obedience, and a scrupulous attention to a puerile kind of propriety, will obtain for them the protection of man; and should they be beautiful, everything else is needless, for, at least, twenty years of their lives. Thus Milton describes our first frail mother; though when he tells us that women are formed for softness and sweet attractive grace, I cannot comprehend his meaning, unless, in the true Mahometan strain, he meant to deprive us of fouls, and insinuate that we were beings only designed by sweet attractive grace, and docile blind obedience, to gratify the senses of man when he can no longer soar on the wing of contemplation.*" [52]
>
> —Mary Wollstonecraft

Let's return to Abbess Hildegard of Bingen once again as an original intellect of the Middle Ages (Fig. 30.1d). Her most popular work in her own lifetime was *Scivias* (Know the Way) which was a series of prose and verse poems presented as visions, in which Christ seems to be speaking through the instrument of the abbess [53]. This work was significant because it was endorsed by St. Bernard of Clairvaux and she uniquely was given rights to speak to audiences which was virtually unheard of at the time. She at one point in this discussion noted that some nuns are equal to church fathers, a claim certainly rejected for centuries and contrary to St. Ambrose and St. Augustine in Church dogma. She was followed by Christine de Pisan another prolific writer in the early fifteenth century who came from Venice to Paris. Christine was an intelligent woman who was left without the dominant male in her life, secondary to premature deaths of her father and husband. Her father was a physician attached to the court of Charles V of France. She was able by her own wits and writing to survive in a man's world by writing an estimated 41 works between 1399 and 1429. She wrote *The Book of the City of Ladies* in 1405 and she wrote of the inspiration of Joan of Arc. She developed a mythic city in which women are appreciated and defended (allegorical to her own situation). Women are actually educated and contribute to society and she used this to encourage women to cultivate useful qualities to overcome the male-dominated misogyny that minimizes women [54].

Following the early modern era, scientific inquiry into the formation of stone disease followed in the late nineteenth and early twentieth century. There were the beginnings of investigations into the difference of stone disease between males and females. Female rights were being expounded by the eighteenth century rather well by such luminaries as Mary Wollstonecraft. Mary was a writer, philosopher, and early proponent of women's rights. *A Vindication of the Rights of Woman* was her 1792 treatise presenting her ideas: "*My own sex, I hope, will excuse me, if I treat them like rational creatures, instead of flattering their* fascinating *graces, and viewing them as if they were in a state of perpetual childhood, unable to stand alone*" [52]. She was hopelessly outmatched in her desires and it would take some time before her notions of equality and fairness would take, in fact, following her death on September 10, 1797, from childbed fever (puerperal fever—unlocked by Ignaz Semmelwies (1818–1865) but again buried secondary to laconic influence of male prejudice at the First Obstetrical Clinic at Vienna General Hospital) [55]. Her husband was the philosopher William Godwin. In January 1798 Godwin published his *Memoirs of the Author of a Vindication of the Rights of Woman* [56]. The world sadly was unprepared for the truth and the realities that one woman could live her life on her terms, and not subjugate her desires to those of masculine norms. The daughter who unwittingly resulted in her demise would inherit both her feminine ideals and her literary talent, Mary Shelley.

She was not the first to clarify such views; we have already noted that one of the key figures of the seventeenth-century transitional views of urolithiasis, Johan van Beverwijck, also wrote a long treatise on the rights of women. Johan went to Padua to continue his medical education. He like Harvey became enamored with the teachings and work of Fabricius. After graduating he returned to Dordrecht and took up practice and continued his anatomical work with dissections. He was a true Renaissance man, becoming a professor of medicine at the Illustrious School, a librarian as well as bibliophile, a civic leader, as well as a prolific writer [57]. He wrote widely to many other scholars such as William Harvey and Rene Descartes [58]. At the end of 1637, Beverwijck wrote a letter to Harvey in which he praised him for his discovery of circulation. Harvey replied to this letter in April 1638 praising, in turn, Beverwijck's treatise on calculi in the kidney and bladder. Harvey described the work as "*learned and elegant, and truly original*" [57]. But it is Beverwijck's treatise in 1639 which was a ponderous 670-page tome called Van de wtnementheyt des vrouwelicken Geslachts (or OF the Excellence of the Female Gender). He essentially argued using historical examples that women are superior to men in human virtues and endeavors [59]. He believed that women should have more freedoms, more access to education, and more influence in society. All in all this was a rather modern and forward thinking from a specialist on stone disease.

Equal Rights

A brief history of suffrage and the achievement of equality by one-half of the world's population is of some historically significant background. The first country to give females the right to vote was New Zealand in 1893. Australia followed in 1902, Finland in 1906, Norway in 1913, the USA in 1920, Britain in 1928, France in 1945, Belgium in 1946, Switzerland in 1971, and Kuwait in 2006 [60]. During the World Wars women were asked and expected to step into the male-dominated workforce and were reluctant to leave their positions following the end of hostilities. Suffrage is broadly defined simply as the enfranchisement of women and implies that they not only gain the right to vote but also to be eligible to run for public office, to place in issues up for referendum, or in other words in a democracy to be nearly equals with males. This is not equality in openness of job opportunities, payment equality for work, nor abilities to participate in any endeavor that one simply chooses [61].

In the USA, Anne Hutchinson was convicted of sedition and expelled from the Massachusetts colonies in 1637 for espousing her religious views. Abigail Adams harangued her husband John Adams during the Continental Congress to "*remember the ladies*" in the laws of the new land. It was not until Frances Wright came to America as the first author to get paid for public lectures that women had any sense of empowerment in 1829.

Lucretia Mott and Elizabeth Cady Stanton became outspoken abolitionists and began to spur women into taking vocal issue with problems in this country before the Civil War. Three hundred people attended the first meeting on women's suffrage at Seneca Falls, New York, in 1848. Lucretia Mott's husband James presided and Elizabeth Stanton wrote the Declaration of Sentiments, which put in place the agenda for women's activism in the political process. In 1851 Sojourner Truth delivered her "Ain't I a Woman?" speech at a women's rights convention in Akron, Ohio. Finally, the Massachusetts legislation granted property rights to women in 1855. Wyoming became the first place in the USA to grant unrestricted suffrage to women in the USA in 1869. Now it was simply a war of attrition, one state after another became the battleground of women's rights. In 1870 the Fifteenth Amendment was ratified which granted women the right to vote in the USA, but there was a long way to go before equal rights were achieved, and arguably they still have some way to go.

The Loss of Gender Bias

Now it is time to turn to what we know about stone disease and females. This too will be done with a view towards history. Stone disease has most certainly afflicted the feminine gender throughout time. In J. Swift Joly's textbook from 1929 he discussed the gender issues in stone disease [62]: "*It is usually stated that stone is much more common in the male than in the female. This is only true of vesical calculus. Stone in the kidney and ureter is comparatively common in the female. Out of 165 cases of renal calculus operated on is St. Peter's Hospital during years 1915-1924, 130 were males and 35 females*" [62]. He next presciently went on to state, "*These figure do not give the true proportion, as the male department of the hospital is so much larger than the female*" [62]. In reviews of the early 1900s we have Brongersma's series of 244 cases of renal stones (139 males to 105 females) [63]. Thurston Holland noted 276 males to 126 females [64]. Hugh Cabot showed 108 males to 46 females [65]. Gottstein in Germany noted 133 males to 80 females. In India during this time McCarrison noted 13.2:1 ratio of males to females, striking but there was a huge flaw in this data. The bulk of stone disease in India were bladder stones and the ratio of bladder to kidney was also 13.5:1 so biasing these numbers towards a large male preponderance [66]. We will come back to these earlier reports and generate a graph of reports from about 1900 to the present. Returning once more to Joly's text, "*On the whole, I think that stone in the kidney is more often met with in the male than in the female, but that difference is by no means so marked as it was supposed to be*" [62]. Is this a misogynous comment or some contemplative speculative abstraction? This leads us to one final comment made by Arthur J. Butt in his 1956 book *Etiologic Factors in Renal Lithiasis* [67]. He begins with "*It has been found almost universally that primary renal calculi are more common in men than in women*" [67]. He noted that the theory falters in pregnancy and he continued, "*The pregnant woman with dilation and stasis of the urinary tract, often complicated by infection, should be very prone to develop calculi. Yet, analysis of collected series of 100,100 obstetrical cases from various parts of the United States reveal only 31 or 0.03% complicated by stone*" [67]. He went on to state that the protective feature of pregnancy was gone within 6 weeks postpartum.

The first remarkable notice that there was something significantly changing came from our own observations at the University of California, Davis, and we presented some preliminary observations on California Databases in the Medical Journal of Australia [68]. We looked into the database because we were being referred an equal number of females with stones compared to males and thought that was unusual. This data was first presented at the VIII International Symposium on Urolithiasis, Cairns, Australia. Upon moving to another institution, this time in New York State, the similar pattern again struck me that there was no male dominance to the disease in my highly referred stone practice pattern. This was subsequently taken and combined with LithoLink's (national laboratory for performing

Table 30.1 The male-to-female ratio of stone formers presenting to a single urologic practice in Upstate New York (left)

Year	CRUS	LL
1995	1.4:1	2.3:1
1996	1.4:1	1.9:1
1997	1.3:1	1.9:1
1998	1.3:1	1.7:1
1999	1.3:1	1.6:1
2000	1.2:1	1.5:1
2001	1.2:1	1.5:1
2002	1.2:1	1.4:1
2003	1.3:1	1.4:1
2005	1.2:1	1.3:1
2006	1.1:1	1.3:1

The database from LithoLink with same ratios calculated over the same 11-year period

24-h urines with stone risk stratification) nationwide database for a presentation at the World Congress of Endourology in 2009. Table 30.1 presents the surgical treatment ratio from a single practice between the years 1995 and 2006. The decline in the ratio from 1.4:1 dropped to 1.1:1. The LithoLink national laboratory in Chicago, Illinois, was also able to provide the numbers of male urines and female urines for the same time intervals. Their ratio was initially 2.3:1 and fell to 1.3:1 during the same 11-year interval. The scatterplot represents a compilation of 65 reports of stone series from 1900 to 2000 that reported on the male-to-female stone ratio (Fig. 30.3). It was also broken down by developing countries versus industrialized countries. This parity in the male-to-female ratio is even more evident, reflecting also that the industrialization of the country has a significant impact upon the gender phenomenon.

Looking into some more recent papers on the topic of gender and stone disease, we find similar findings. Hiatt and colleagues in California noted that from 1964 to 1972 in the Northern California Kaiser System, the male-to-female ratio was 1.5:1. This number jumped to 3:1 from 1970 to 1972 and was down to 2.7:1 from 1971 to 1975 [69]. Scott in an X-ray study of people in a community in Scotland with random sampling showed a male-to-female ratio of 1.03:1 [70]. Other prevalence studies show the same pattern. In rural Thebes, Greece, 422 subjects were studied and a 15 % incidence of stones was found. The prevalence by gender was slightly more males than females but the odds ratio was insignificant [71]. In an American rural study between 1992 and 2008 Penniston and coworkers noted a drop in the male-to-female ratio during this time frame from 1.4:1 to 1:1 [72]. Scales reported similar findings from a Nationwide Inpatient Sample study of databases. They noted a change from 1.7:1 to 1.3:1 from 1997 to 2002 [73]. Lieske et al. also noted a drop in the gender ratio to 1.3:1 from Rochester, Minnesota [74].

Now we must consider this from a historical perspective and always in history we must question the sources. Perhaps stone disease did afflict females more commonly than we thought because the data collections themselves were biased. This is certainly the case in some instances. Women and men though did have different roles and lifestyles throughout most of the past. Diet, exercise, fluid ingestion, types of fluids ingested, and stresses have all been referenced by the numerous authors who have sought to define the gender differences. There is a robust research literature however on the influence of male androgens on the development of stone disease in animal models, all based upon the presumption that males are more prone to kidney stones than women [75]. This literature is vast and does suggest that testosterone does play some role in the development of calcium-containing stones in rats and mice. There is even a recent study from the Middle East on androgens in male stone formers whose very title of the paper suggest bias, *Determining role of gonadal sex hormones in the pathogenesis of urolithiasis in a male subject- a document for male predominancy (case study)* [76].

Conclusions

> "*Goodness, I hope if heaven is crowded, that all the rest of humanity will be cast out to make room for the doctors.*"
>
> —Agnes Reid (1874)

As to the fact that stone disease afflicted women, there can be no doubt, and the exact incidence

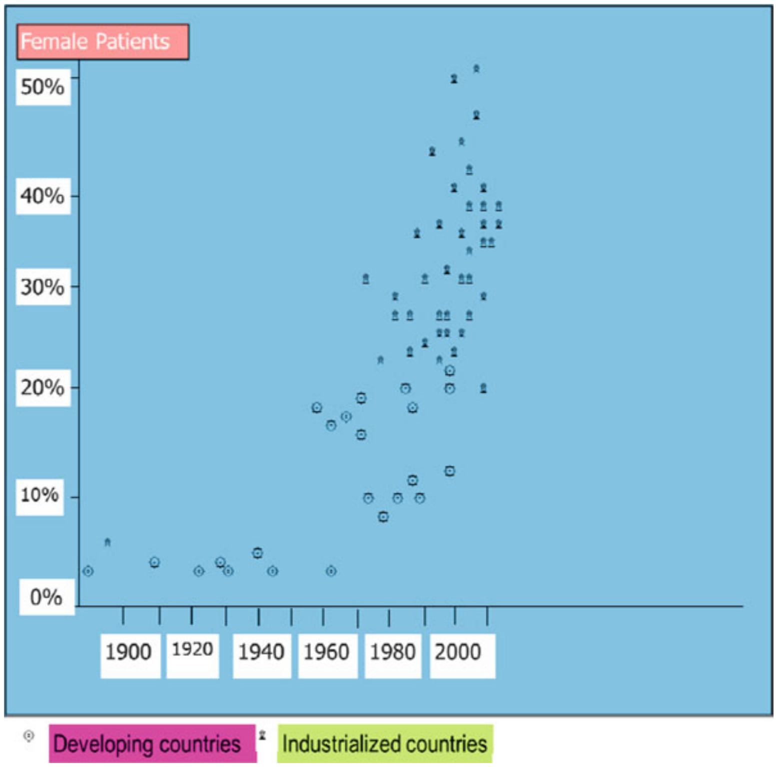

Fig. 30.3 A scatterplot of 70 papers from the turn of the twentieth century breaking down the papers by countries that are developing versus those that have fully industrialized

from ancient sources is untrustworthy at best and minimizes the suffering in females. We have presented under the chapter of Renaissance of Urolithiasis the case of self-performed perineal lithotomy by a Dutch male named Joannes Lethaeus (de Doot) and were impressed with his fortitude and ingenuity. There is a case in realm of kidney stone disease that just might one-up de Doot's surgical endeavor. This case was described anonymously in the Philosophical Transaction in 1695–1697: "*He seems either not to have met with, or not to have believed that extraordinary Case in Cœlius Rhodiginus var. lect. L. 3.c.12 of a Woman, who having for a good while been afflicted with a load and pain in the Region of her Kidnyes; scratched with that rage and impatience so long with her Nails, till she made a Wound so large and deep, as to discharge eighteen Stone magnitudine quanta in tefferis visitor*" [77].

Perhaps the best epidemiologic strike against male-dominated incidence of stone disease comes from the literature that historically was truly linked to maleness for almost the totality of history itself, warfare [78]. In December 2010 the Armed Forces Health Surveillance Center published its monthly report on issues affecting the troops in the military. This report though focused on Women's Health Issues [79]. Let's begin by quoting their overview, "*Urinary stones can cause debilitating morbidity that impairs the operational effectiveness of affected members of the U.S. Armed Forces. This report describes a 'gender shift,' i.e., the narrowing of prevalence differences between men and women, similar trends described in the U.S. civilian population. Rates of incident diagnoses of urinary stones increased in the active component during the past decade-particularly among females. On average, 60 service members were medically evacuated from combat zones each year during the period. Service members with a history of urinary stones should be counseled on reducing* *risk, particularly in the deployment setting*" [79]. This report comes from data collected for the decade of 2001–2010. During this period 61,587 active component members received 84,055 diagnoses of urinary stones. The overall incidence rate was 58.9 per 10,000 person-years, and they noted that the annual incidence rate increased 15.2 % from 2001 to 2010. Most stones (86 %) were upper tract stones (kidney or ureter) and this also increased 38 % [79]. This is fascinating, "*among the service branches, the highest overall incidence rate (79.0 per 10,000 patient-years and the largest relative increase in annual rates (34%) affected the Coast Guard members; the lowest incidence rate affected Marine Corps members (42.4 per 10,000)*" [79]. Perhaps they had read Copland Hutchison's supposition on sailors and stone disease [80]. They noted that the incidence rates were very similar between females and males (58.6 per 10,000 female versus 59.0 per 10,000 in males). Another finding was as follows: "*However, during the surveillance period, annual rates increased by large percentages in every age group of females, but by relatively small percentages (or not at all) in various age groups of males*" [79]. Medical evacuations were also tracked in this report. They also reported that 625 soldiers were medically evacuated for stone-related encounters during these 10 years. They conclude with the following: "*Urinary stones are a significant military medical concern because they are associated with decreased military operational effectiveness (e.g. lost duty days, medical evacuation) and may be precipitated by environmental stressors common to military training and operational settings. Particularly during physically rigorous operations in hot, dry environments (such as Iraq and Afghanistan), U.S. military members may be at high risk of dehydration, decreased urine output, concentration of the urine, and urinary stone formation*" [79].

Female physicians have not obtained acceptance until very recently, and the debt owed to those women from ancient times is enormous. Beginning in the twentieth century, the USA had only 4 % of medical school graduates that were women (1905) [81]. In the 1970s this rose to 7 % and by 2004 this number had risen to 24 % [82]. The number of women that are now medical students is 49 % and there are ten female deans, or heads of medical schools, in the USA [82]. Women have come a long, long way from the days of fourth century BCE. Athens. In 1923 an article appeared in JAMA regarding urology in women; Stevens wrote an early interesting study of 200 nonpregnant women who had urinary symptoms and found that 70 % of them were entirely from urinary tract etiologies [82]. The title was somewhat misleading because it is regarding gynecologists doing many of the things that urologists should be doing. Urologists are those specialists that primarily diagnose and treat urinary tract diseases, and because the bulk of these were male, the penetration of this profession by females has been somewhat delayed [83]. Helen Wingate was one of the first women in urology in England who worked at the Glasgow Royal Infirmary [84]. Elisabeth Pauline Pickett was the first American board-certified urologist in 1962 [85]. Christina Hill was the first female urologist in Canada in 1969 [86]. Women have progressively added to the wealth of knowledge of urinary diseases in general [87]. First and last female authorship has increased from a mere 2.7 % in 1979 to 26.5 % in 2009, indicating a rate increase that exceeds the rate of increase in females in urology itself. The slow trickle of females interested in genitourinary disease has been growing [88]. But it appears that the overall care of patients, for instance, kidney stone patients, whose metabolic and surgical management often comes under the urologist's purview, seems to be attracting women into urology [89]. Urology did not even merit its own category in a year 2000 survey of women physicians but was clumped in the 1.2–3.2 % of women who were in surgical subspecialites [90]. But women appear to be a contended bunch with the chosen profession of urology. Of 244/365 (69 %) board-certified female urologists who responded to a survey, 87 % were happy with their decision to enter urology (the highest among women in surgical subspecialties). Forty-two of those surveyed had done postgraduate fellowship training, some in endourology and stone disease [91].

Dr. Margaret Pearle, M.D., Ph.D., is a female urologist and head of Endourology and Stone Disease at the University of Texas, Dallas. She wrote the chapter on Urolithiasis from the Urologic Diseases in America Project and has become one of the word's experts on urolithiasis [92]. Peggy is also the past president of the R.O.C.K. Society (which we've discussed previously) and the author of the chapter on Urolithiasis in Campbell's Urology clearly representing the best of the feminine gender in the care and management of stone disease [93].

Throughout much of the latter half of this textbook, we have referenced several authors multiple times, but one stands out, John Green Crosse (1790–1850). His 1835 Jacksonian Prize treatise on stone disease was a remarkable achievement. He utilized over 2,700 references showing him to be a towering intellect and a prodigious bibliophile. It is a tribute to his dedication to stone disease that his granddaughter Dr. V.M. Crosse wrote his biography in 1968 [94]. He would be happy to know that the previously closed doors of the medical profession are almost freely open to those women who seek similarly as the Hippocratic physicians of ancient Greece "*whatever houses I may visit, I will come for the benefit of the sick…*" [13].

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31 The Urologist's Guide to the Galaxy

Introduction

The title of this paper comes, of course, from the late Douglas Adams's famous work of science fiction entitled "*The Hitchhiker's Guide to the Galaxy*," and this is appropriate because our actual knowledge of stone formation in space is shrouded in secrecy and speculation [1]. But the science of urinary supersaturation, physiology of bone resorption, and many of the deleterious effects of prolonged zero-gravity exposure are well described. We are now entering what many perceive as "The Century of Space Exploration," and it behooves those of us interested in urinary calculus disease to review our current understanding of what lies ahead, review related hazardous environmental experiences in order to form some realistic expectations as mankind approaches Kardashev's level I civilization [2]. Another possible reason for this exercise for many, like the author, is an absolute fascination about the potential for continued space exploration, sparked by Neil Armstrong's memorable descent upon our moon [3].

Science Fiction

"*There is no way back into the past. The choice is the Universe- or nothing*." stated H.G. Wells. Space rock 84,001 is a piece of Mars ejected an estimated 3.6 billion years ago and landed upon this third planet from the sun at the South Pole approximately 13,000 years ago. It appears to have organic tubes that indicate the strong possibility that there was life on that planet some time ago. Our interest in space is as old as the genre of science fiction itself, and quite probably older. We are currently in the midst of intense interest in Mars and some of Jupiter's moons as they might hold basic knowledge on the origins of life. In addition, it has been postulated that our home world is prone to periodic and perhaps sudden catastrophic impacts from space debris that would behoove a knowledgeable species to figure out methods of space exploration, colonization, and/or expeditious transportation.

Our current problem with these science fiction-like endeavors is the current costs of placing payloads into outer space. It has been estimated that 800 million dollars per space shuttle launch which can carry about 27 ton costs us about $15,000 per pound (or roughly twice the cost of gold). There are promising technologies that quite likely will solve these huge financial hurdles and allow us to rapidly and far less expensively have access to near-Earth orbit. These include the Lockheed Martin X-33 VentureStar, NASA's collaborative hypersonic scramjet, the X-43A (recently hit Mach 10), and my personal favorite, the "space elevator." Using nanotechnology, carbon nanotubes might be created that would allow a fixed terrestrial point on the equator to be attached to an orbiting platform that would literally run payloads into outer space at a fraction of current costs. If any of these technologies (and assuredly others not listed) manages to

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prove feasible, the doorway to space will become wide open and our exploration of space will shift into high gear. In fact, the probability that this might be so has prompted many scientists to prematurely call our current century "The Century of Space Exploration."

There are many hazards to space existence for terrestrial humans. The focus of this discussion will be upon the known risks of urolithiasis formation in outer space. The published literature will be reviewed, the physiology summarized and unpublished, but widespread speculations shall be aired. In the end, our knowledge is not exact, and the methods of dealing with colic in space are unknown and as speculative as science fiction itself.

Science Fact

Early in the clinical literature of urolithiasis, it was documented that humans who are incapacitated and bed ridden are prone to kidney stones. In 1922, Paul from Toronto reported on 20 cases of nephrolithiasis occurring in men aged 22–37 (average 28.5) who developed renal calculi following war wounds. The average time from the wound to the first symptoms of stones was 17.7 months. All patients had extensive injuries including osteomyelitis. Most of these patients were bedridden for prolonged times [4]. Fowweather followed by Pulvertaft both indicated that recumbency appeared to be the critical problem associated with calcium stone formation, not the degree of trauma [5, 6]. The primary event increasing the risk of nephrolithiasis appears to be an acute mobilization of calcium from the skeletal reserves [7]. In some patients, hypercalciuria may be pronounced [8]. In these patients, indwelling Foley catheterization is also common and subsequent bladder infection makes upper tract seeding commonplace. Recurrent urinary tract infection therefore changes the primary stone risk in these patients with high urinary pH with the potential for ammonium production to form struvite stones (magnesium ammonium phosphate hexahydrate) [9]. In current practice with the emphasis on early mobilization and vigorous rehabilitation, no patients except perhaps those with global trauma (i.e., multiple organ-injured individuals) run this risk. One current investigation on immobilization-related hypercalcemia in a mere five patients tried to ameliorate bone mineral loss [10]. In all of this immobilized group, the hypercalcemia during 3 months of observation could be reversed by administration of low-dose pamidronate (10 mg). In a review by Gordon and Reinstein, a discussion of common secondary problems associated with the management of complex trauma victims revealed that urolithiasis was a significant problem. In addition, the costs in managing this secondary problem were significant [11]. It would seem reasonable despite a paucity of published data that immobilized patients are at higher risk and maintenance of adequate hydration would be a minimal recommendation. The use of bisphosphonates is more uncertain but indicated if hypercalcemia or urolithiasis develops. A final area of consideration is the effect of physical activity on calcium balance and calcium requirements and upon bone mineral mass. Because of the aging population and the increasing risk of osteoporosis-induced risk of presbic fractures, a significant volume of research is becoming focused upon these issues. In some studies, physical activity has been noted to have a more profound role in affecting enhanced bone mineral density prior to puberty [12]. The need for greater research and the potential for physical activity itself to have an effect upon calcium balance is critical, and the application of these findings to zero-gravity environments is just beginning [13].

A corollary to the immobilization-related hypercalcemia and stone formation scenario is the possibility of placing humans in microgravity activity in outer space. With the advent of cooperative international endeavors such as the Space Station, plans for a manned mission to Mars, and the real probability that China might attempt a mission to the moon, these considerations have assumed a more vigorous scientific scrutiny. The physiologic changes that occur to astronauts exposed to microgravity during spaceflight have been increasingly investigated. Body fluid volumes, electrolyte levels, and bone and muscle undergo significant changes as the body adapts to the weightless environment. There are both short-term space missions similar to those of Gemini, Apollo, and space shuttle flights and long-term missions such as Shuttle-Mir or Skylab [14]. In the former short-term space missions, negative calcium balance with bone mineral loss and associated hypercalciuria was noted during Gemini, Apollo, and space shuttle missions [14]. Additional alterations include elevated urinary phosphate, decreased fluid intake secondary to early flight space sickness (associated nausea and vomiting) with resulting decreased urinary volume, and rising formation product [15]. Citrate has been shown to fall during spaceflight [16]. Whitson and coworkers have demonstrated that astronauts are at greater risk of forming calcium oxalate, calcium phosphate, and uric acid stones. In follow-up investigations, this same group studied more carefully six male astronauts with a mean age of 42.5 (range 36–49 years old) flying space shuttle missions of 11–16 days [16]. Urine specimens were collected before, early in the mission (2–4 days), late in the mission (10–13 days), landing day, and 7–10 days after landing. Nutrition recommendations were rigorously controlled. Urine volume declined during the early flight but tended to equilibrate by postflight measurements. Urine output declined by 22–52 % during spaceflight. Urine pH had a tendency toward increased acidity (lower pH) which also normalized by 7–10 days postflight. Urinary calcium levels increased for all members with individual variation being large (38–253 mg/d). Calcium excretion continued to increase during the flight. Urinary potassium was less during the early flight and urinary citrate was lower during the flight but neither was statistically different. The relative supersaturation of calcium oxalate, brushite, sodium urate, and uric acid all rose during early spaceflight. The calcium oxalate and brushite supersaturations remained statistically elevated throughout the entire spaceflight [16].

Whitson and colleagues further speculate that dietary factors of the astronauts also play a role in risk for urolithiasis formation. Fluid restriction and protein and calorie ingestion all increase urinary calcium and uric acid concentrations while decreasing urinary citrate. Dietary sodium can also promote renal calculous disease. Diets high in potassium and magnesium may have beneficial effects [16]. Zerwekh reviewed this metabolic data and generated specific nutritional recommendations for crew members on longer space missions. Pharmacologic intervention can raise urinary volumes, diminish bone losses, and prevent reductions in urine pH and citrate levels [17].

There exists one published article suggesting that some cosmonauts have in fact formed stones during space missions [18, 19]. Another report from NASA's Life Sciences Division suggests this to be a real probability [20]. In Pak's earlier investigations in stone formation by astronauts, he suggested that stone risk factors among applicants for spaceflight programs were environmental in origin [21].

Stones in Space

Spaceflight is a hazardous activity. There are published well-documented investigations into the pathophysiologic problems encountered [22]. In-flight medical events for US astronauts during the space shuttle program from April 1981 to January 1998 show a 42 % incidence of space sickness but no definite reports of urinary colic and/or urolithiasis. Medical events reported from Russia's Mir from March 1995 to June 1998 likewise fail to reveal any stone events. But space exploration and manned flights are still infrequent compared to terrestrial explorations in other hazardous environments, such as deep sea and polar. Antarctic databases on health hazards also disclose no episodes of evacuation for urinary colic. The incidence of evacuation from US submarines from 1993 to 1996 reveals 23 episodes of acute colic and stone passage out of 332 total emergency evacuations.

Stone disease represents a real risk to our human habitation in micro- or zero-gravity environments. The physiology behind this increased risk is well known, and preventative strategies have been developed. The fact that stones in space have not been reported does not mean that they have not occurred. Astronauts as well as pilots in general have an obvious bias against coming forward in reporting these episodes, grounding. In addition, the system would find that the cost of training specific individuals might outweigh the risk of stone formation in the "highly selected" individuals and efforts to keep them flying might outweigh and justify avoiding reporting. But stone disease in space is potentially serious, especially if exploration expands and extraterrestrial work environments are created that would prolong microgravity exposure times. NASA's "Bioastronautics Roadmap" calls renal stone formation "Risk 4" [23]. The National Space Biomedical Research Institute calls stone disease "Risk 12." One published article only suggests that some cosmonauts have, in fact, formed stones during space missions. Detailed data from 79 US space missions, involving 219 person-flights, and 175 astronauts do demonstrate 23 genitourinary problems (1.2 % or 0.07 incidence per 7 days). Conflicting data exists regarding actual space mission risk and stone incidence during submarine duty, but all would agree that the risk of stone disease in space is real. Attempts to evaluate both diagnostic and therapeutic interventions are being pursued actively and the funding for such endeavors is ongoing. As mankind strives to gain access to the final frontier of outer space, hazards must be assumed and methods for adapting to these risks must be found.

In 2008 a presentation by NASA scientists occurred at the 2nd International Urolithiasis Research Symposium in Indianapolis, Indiana. The authors began, "*U.S. spaceflight experience to date from early space vehicles (Mercury, Gemini, Apollo, Apollo-Soyuz) to Space Transportation Systems (STS-Shuttle) to long duration space platforms (Skylab, NASA-Mir, and International Space Station) cumulates to approximately 30,000 crew-days, >80 crew-years. On Shuttle missions from STS-1 to STS-108 (106 Shuttle flights) cumulating in 5496 flight days, 588 of 607 (97%) participating crew members experienced some medical symptoms*" [24]. They went on to note that a whopping 74 % of astronauts developed urinary symptoms. In this paper they point out a previous study that noted fourteen postflight stones formed and one Russian cosmonaut who developed a stone on the Salyut that resulted in an emergency evacuation and return to Earth. This person developed ureteral colic for hours until his return, but he subsequently passed his stone without intervention; this stone was not recovered so the type is unknown. The others included, "*Eleven U.S. crewmembers have had 14 urinary calculi following their spaceflights, all after the missions less than two weeks in duration*" [24]. They also present that a diagnostic modality apparently is available on the International Space Station; "A flight class I, rack-mounted Philips/Advanced Technologies Laboratory model HDI-5,000 ultrasound imaging unit" is available. These scans, if necessary, are performed by a Crew Member Medical Officer (CMO). Apparently they have ground guidance from a physician team consisting of a radiologist and a urologist [24]. They conclude with the risks of developing stones in space posing a significant risk. They state, "*A properly developed approach to selection, monitoring, and preventive medicine with effective countermeasures, along with a readily implementable protocol of early imaging diagnosis and minimally-invasive contingency intervention, should prevent GU issues, such as urinary calculi from having a significant mission impact for exploration-class space flight*" [24]. Like so much technology that has evolved from our current infancy-staged space applications, one can only hope that urolithiasis, its care, management, and prevention will also fall to the knowledge that is obtained from these ongoing endeavors [25].

Arthur C. Clarke stated, "*Two possibilities exist: either we are alone in the Universe- or we are not. Both are equally terrifying.*"

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32 Towards Keeping the Hippocratic Oath (Six Sigma)

Introduction

> "*In some way, it may be in the nature of surgery itself to want to come to grips with the uncertainties and dilemmas of practical medicine. Surgery has become as high tech as medicine gets, but the best surgeons retain a deep recognition of the limitations of both science and human skill. Yet still they must act decisively*." [1]
>
> —Atul Gawande (2002)

There are many individuals who write about future technologies that are expected to transform our societies. Many of these are merely speculative in nature without considering the potential upheaval that these advanced technologies will have upon every aspect of our societies, including the way we treat urolithiasis. For instance, our last major historical upheaval was the Industrial Revolution which resulted in the fall of bladder stones but the rise in renal stone disease. During this time frame, we have gone from a "craftsman-oriented" economy to a "mass-produced" type of economy. We have gone from a "community-centric" environment to a "globally centric" one [2]. We have seen the rise and fall of innumerable hegemonies of government to a more pluralistic kind of control [3]. Stone disease has proliferated and rapidly increased in incidence and prevalence throughout much of the world.

Without question, the next major influence upon mankind, that enabling technology which will be capable of catapulting us again to the next level are intelligent technologies (IT). In order for us to prepare for tomorrow, or for that matter, know which pathways to follow, it is incumbent upon us to know what is happening with technology. For life in general, medicine more relevantly, and to urolithiasis specifically, there is a "*growing mountain of research*" threatening to engulf us. How can we as caring and compassionate physicians (*sic* assumed) continue to be masters of it all? Socioeconomically, there is no question that the financial forces currently at work around the globe are threatening to consume all of the gross national products of many countries.

We need to develop the historical background for you in this review to make the technologic leaps necessary to master the maelstrom to come. Starting with digital computer technologies, working through artificial intelligence, encompassing biotechnologies that remain at the core of medical practice, and ending with nanotechnologies, the intent will be to give a historical *tour de force* for the next decade, perhaps even the next century. By looking backwards as to how we arrived at this precipice on which we are now perched, it is hoped that you, like Winston Churchill, might see further into your futures.

Principles of Change

Someone once said that the only constant is change. Sir Karl Popper has written elegantly about the basics of scientific change: "*The critical attitude may be described as the conscious*

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attempt to make our theories, our conjectures, suffer in our stead in the struggle for the survival of the fittest. It gives us a chance to survive the elimination of an inadequate hypothesis- when a more dogmatic attitude would eliminate it by eliminating us" [4]. But how can anyone predict the future? In fact, the literature is strewn with the flotsam and prophesies gone awry. For instance, Bill Gate's 1981 classic, "*640,000 bytes of memory ought to be enough for anybody*." Ken Olson in 1997 stated, "*There's no reason for individuals to a computer in their home*." Better for our purposes is Yogi Berra's quip, "*It's tough to make predictions, especially about the future*" [5].

No one can accurately predict the future. New developments and new discoveries are always capable of rewriting what we think we know. Chance certainly plays a role and no one could have foreseen the impact of the World Wide Web on our society when Tim Burners-Lee wrote the code for CERN in 1991 (note: that's not that long ago!). So why spend so much time on something as fickle as the future? You can think about what has happened to us by a lack of foresight as we've already alluded to, or you can consider the scenario of nuclear weapons as an example. Would you rather develop a monster before you consider how to make a cage? Long-term forecasting is not futile when carefully considered concerns remain the focus. To quote Drexler, "*In a race toward the limits set by natural law, the finish line is predictable even if the path and pace of the runners are not*" [6]. David Hume, the eighteenth-century Scottish philosopher, introduced in 1737 the notion that observations cannot logically prove a general rule; rationalism cannot be trusted [7]. By 1945, Bertrand Russell presented the twentieth century's response to the "*growth of unreason*" and the death of empiricism to vault us into our modern era [8]. This thinking has led us to our recent predilection of future speculation and the scientists' favorite science philosopher Karl Popper phenomenon of evolutionary process of development [4]. Technologic variations and advancements are quite often deliberate, plodding, and crude in comparison to the science that lies behind them. Edison tried virtually every product on the planet before settling upon tungsten as the filament for his incandescent light bulb [9]. Charles Goodyear tried everything to make unacceptable rubber into the moldable, durable substance we today use in tires by a chance drop of sulfurized rubber in his lab. The point is that engineering the marvels of tomorrow's technology is methodical and predictable in a fashion in that it is evolving. Future breakthroughs result in rapid progress. Progress evolves through cycles of design, calculation, criticism, redesign, and construction. So, forced by competition and testing, science evolves towards more power and accuracy. Efforts to predict the engineering achievements started way back in classic Greek technology. Leonardo da Vinci in his collected works called the *Codex Atlanticus* made projections using detailed drawings regarding the ability of machines to improve upon motion and power control with machines [10]. He designed an earth-mover to make canals that were never built. He designed a robotic man at the age of 30. He utilized a design he envisioned at the age of 26 to power his automated soldier or knight. This device used a front wheel drive, rack-and-pinion automated cart to provide both the power and the mobility that his robot would require. Leonardo designed a chain-drive system that would remain unbuilt for almost three centuries and the bicycle. He failed to build an aircraft because of his inadequate understanding of modern aerodynamics and lift. But this lack of scientific knowledge certainly did not stop him from designing these machines [10].

Prior to concluding this section of the introduction, there are three key publications that are worth reviewing. The first is Vannevar Bush's 1945 article that appeared in the *Atlantic Monthly*, entitled "*As We May Think*" [11]. Bush was an MIT-trained engineer with a particular aptitude for math. He was a young professor at Tufts when World War I broke out. Bush developed a device that would use magnetic fields to detect submarines. He traveled to Washington in May of 1917 to meet with the new director of a group of scientists advising the government, the National Research Council (NRC). After the war, Bush matriculated back to MIT's electrical engineering department. He became interested in analog computers to solve complex equations and by 1931 he completed the first differential analyzer. He also proposed and built a machine for the FBI that could review 1,000 fingerprints per minute which he called a rapid selector. In 1937, Bush became the president of the Carnegie Institution with a then $1.5 million annual budget for research. His prestige rapidly increased and by 1940 Roosevelt called on him to create a new national organization for scientific military research called the National Defense Research Committee (NDRC). Bush was made the first chairman and given a direct line to the White House. By 1941 the Office of Scientific Research and Development (OSRD) was set up and Bush became its director [12]. Bush became intimately involved in advising Roosevelt about the Manhattan Project. Colliers magazine hailed Bush as the "man who may win or lose the war". By war's end, Bush dreamed about a national science group and the National Science Foundation was created in 1950 [12]. He published "*As We May Think*" in the Atlantic Monthly. This article describes a whole host of technologies that did not then exist. He describes a theoretical machine called a "*memex*." This was to be a multipurpose intelligence extender. The memex would be a repository of general information that a user could call upon for facts and figures [11]. His description is hauntingly close to modern hypertext and the Internet. In 1960, Ted Nelson, who coined the term hypertext acknowledged his debt to Bush.

The second article was first presented on December 29, 1959, at the annual meeting of the American Physical Society at the California Institute of Technology. It was subsequently published in the February issue of Caltech's *Engineering Science* by the Nobel laureate Richard P. Feynman. The title, typical of Feynman, was inauspiciously called "*There's Plenty of Room at the Bottom*" [13]. He stated that he wished to talk about "*the problem of manipulating and controlling things on a small scale*" [13]. He goes on to state that an enormous number of technical applications would arise from such a technology and that there were no fundamental reasons of physics preventing its development. He proceeded in the ensuing 11 pages to recount the possibilities of molecular engineering, which heretofore have been unheard of. He then continued with the physics of such machines including miniaturization, lubrication, supply, and demand. He concluded with a discussion of "*rearranging the atoms*" themselves. He speculates the complexities involved with quantum physics at the atomic level, but concludes "*The principles of physics, as far as I can see, do not speak against the possibility of maneuvering things atom by atom. It is not an attempt to violate any laws; it is something, in principle that can be done; but in practice, it has not been done because we are too big*" [13]. He stated that it is his opinion that such a *nanotechnology* (*sic* word mine) cannot be avoided in the future. And he created a cash award of $1,000 for school kids and engineers to start this technology: "*I do not expect that such prizes will have to wait very long for claimants*" [13]. But Feynman never saw the emergence of this technology in his lifetime. Tom Newman, a Stanford electrical engineering grad student, used electron-beam lithography to transcribe the first page of Charles Dickens's A Tale of Two Cities onto a square 1/160th of a millimeter on the head of a pin [14]. In fact, it was not until the Bush Administration was leaving office that Clinton enacted the National Nanotechnology Initiative in order to speed basic research.

The final article which fittingly concludes this section while also introducing the next appeared in *Electronics* in April 19, 1965, by Gordon E. Moore. The article was called "*Cramming more components onto integrated circuits*" by the then director of Research and Development of Fairchild Semiconductor [15]. He started this article with the prophetic words: "*The future of integrated electronics is the future of electronics itself*" [15]. Moore talked about the future of intelligent technologies as no one before had; he speculated about ubiquitous computerization. He stated that computers of the future will be distributed, not centralized. He predicted that the machines of the future would be built at lower costs and with faster turnaround because of acceleration of power and capacity. He based his observations on 25 years of experience in the miniaturization of electronic components. He predicted that integrated electronics would become generally available throughout all of society, performing many functions that presently are done inadequately by high-cost systems. He predicted that silicon would most likely remain the basic material of semiconductors and the key to this expansion. He finally warmed to his topic in talking about graphs and curves he had generated. For simple circuits, he said, the cost per component was nearly inversely proportional to the number of components. He demonstrated cost curves from 1962, 1965, and 1970 showing a 1/10 reduction in cost but he didn't stop there. He predicted that if trends hold, and he saw no reasons why they should not, then within 10 years an integrated circuit with 65,000 components could be achieved for minimum cost and the size will be reduced to about ¼ a square inch. He also predicted the heat generated by tens of thousands of components in a single silicon chip. He also noted that the shrinking dimensions on the integrated structure would result in operations at higher speeds for the same power per unit area [15]. Thus, in one neat and tidy paper, Moore predicted the coming era of intelligence technologies. All subsequent works on the future of these technologies continued Moore's prescient observations and his doubling times have eroded, not held constant. Technology is advancing faster than Moore even conceded.

So the stage is set; the future is capable of being anticipated within the limits of constrained technologies. The only thing missing is the amalgamation of converging technologies. This will be the foundation of the next section.

The Law of Accelerating Returns

The goal of this section is to convince you that all of our previous recorded history regarding technology in general and digital intelligent technologies in particular are converging. Convergence is that phenomenon when the focal capacity in any given area meets at commonality. The commonality of all of these technologies is life itself. Lest you think that believable science is being stretched into science fiction, a wide variety of resources will be utilized that are available to you, the reader (disbeliever or believer), so that you can check on the *sources*' validity of anything that this author is writing about. Ray Kurzweil, the entrepreneurial scientist who developed digital software for the music industry, has published several books on this subject. He has a website and technologic discussion blog with graphs regarding human technologic advancement as the fundamental preposition and he devised the law of accelerating returns. K. Eric Drexler published "*Engines of Creation*" that has already been mentioned. He suggested that mankind was approaching a new frontier of technologic advance based upon nanotechnology that would be fostered by advances in intelligent technologies [6]. In June 2002 our own National Science Foundation (introduced by the way by Vannevar Bush, recall "*As We May Think*") met in Arlington, Virginia, and reported upon "*Converging Technologies for Improving Human Performance*" [16]. They focused on specific issues that are rapidly advancing in four areas of scientific research. These included nanotechnology, biotechnology, informational technology, and cognitive science. In addition, NASA (National Aeronautics and Space Administration) has now had yearly scientific workshops and meetings specifically addressing the convergence of technologies and the applications to space exploration. By reviewing each of the salient pieces of these science facts, it is hoped that you too will feel the growing excitement that has spawned *so* much negative or "conservative" scientific response by some serious researchers. Francis Fukuyama has publicized his views of the perils of converging technologies in "Our Posthuman Future: Consequences of the Biotechnology Revolution" [17].

Ray Kurzweil is a graduate of MIT and among the many innovations he has invented include reading machines for the blind, music synthesizers used by such performers as Stevie Wonder, and speech-recognition technologies. His alma mater, MIT, named him the inventor of the year in 1988. Carnegie Mellon bestowed their top science award to him in 1994, and he won the

American Publisher's Award for Most Outstanding Computer Science Book in 1990 for his "*Age of Intelligent Machines*" [18]. It was in fact Kurzweil's thinking and findings that launched Sun Microsystems founder Bill Joy to write the "highly" thought-provoking article in the journal for technophiles *Wired* called "*Why the Future Doesn't Need Us*" [19]. In this excellent observational science article, Joy argued that our technologies are becoming increasingly complex and that public participation in advancement has all but been eliminated. He outlined a scenario where our technology has become *so* sophisticated that it endangers the human species. This brings "shades" of Terminator to our consciousness and from a very gifted scientific insider. What has Joy so spooked is a well-fabricated and illustrated march to "massive leaps" in technologic advancement by the convergence of intelligent technologies [19]. Kurzweil in his writings took all of mankind's technologic advancements and attempted to do what Gordon Moore had done for just microprocessors, but he overlaid them in graphic formats to see what is happening. He then explained that almost every aspect of modern technology is rapidly expanding at exponential growth rates. The exception is computer or intelligent technology itself which is expanding at a double exponential rate. That is to say, that its rate of growth is itself exponential!

Mankind's first technologic steps, "sharp-edged tools, fire, and the wheel," took tens of thousands of years to develop and master. By 1000 AD progress was much faster. By the nineteenth century, there were more inventions than *all* of recorded history previously. The first 20 years of the twentieth century saw more advancement than the entire nineteenth century. Now, huge technologic advances change the whole world in just a few years. No one, closely looking at the pace of technologic development, would argue that we could easily have a 1,000-fold advance very, very quickly.

Kurzweil uses example after example to argue that we have arrived at the precipice of a *singularity* based upon the study of exponential growth of our technologies [20]. Singularity, according to Ray, is a point where technologic change is so rapid and profound that a rupture in the fabric of human history is probable [21]. This folks is what has Bill Joy and a whole host of other very smart scientists concerned by the convergence of our technologies. John Von Neumann, one of the great mathematicians of our time and a founding father of artificial intelligence technologies, stated in the 1950s, "*the ever accelerating progress of technology…gives the appearance of approaching some essential singularity in the history of the human race beyond which human affairs, as we know them, could not continue*" [22].

This year, Oak Ridge's Titan computer (Nvidia and Cray) blasted past IBM's massively parallel processing supercomputer Sequoia at the Lawrence Livermore National Laboratory at 17.59 petaflops (Sequoia a paltry 16.32 petaflops); a petaflop is a quadrillion calculations per second [23]. Kurzweil believes we will achieve human brain capability with our computers for just $1,000 by 2023 and for 1 cent by 2037 (this is 1×10^{16} cps). Pooled human brainpower from every living human being on this planet should be achievable by 2045 for $1,000 and by 2059 for just a penny (i.e., 1×10^{24} cps) [20]. Titan has weighed in at just little over 1/10th as smart as a single human being. The question to be answered is: What will all of this intelligence technology be used to do? To quote from Drexler's book:

> "*In the last century we have developed aircraft, spacecraft, nuclear power, and computers. In the next we will develop assemblers, replicators, automated engineering, cheap spaceflight, cell repair machines, and much more. This series of breakthroughs may suggest that the technology race will advance without limit. In this view, we will break through all conceivable barriers, rushing off into the infinite unknown…*"
>
> (Drexler, Chap. 10, Limits to Growth) [6].

What is happening in the real world of surgical practice in these regards? Stone disease has several surgical alternatives: endoscopic (retrograde ureteroscopic methods utilizing the holmium: YAG laser vs. percutaneous transrenal methods that can use either lasers or ultrasound or mechanical methods), shock wave lithotripsy (high-energy waves generated outside and beamed into the body to break up stones), or in complex scenarios the use of robots to perform what in the past were open operations. The methods that we've alluded to throughout this textbook have evolved and followed the trends that we have just been talking about. Celsus gave way to the Marian approach, which in turn gave way to the lateral perineal lithotomy, which gave way to Civiale's pioneering lithotrity, which became obsolete with Bigelow's litholapaxy, which has been antiquated by the holmium: YAG laser, and bladder stones themselves became a historical oddity by improved dietary nutrition, and open renal stone surgery is rarely indicated any longer, despite the rapid increase in new stone sufferers. The literature is nearly impossible to keep up with, the newer technologies are hard to place into perspective, but the abilities of our technology to change what we are doing currently is ever more likely [25]. But the technology itself is helping keep track of the literature; via the Internet a massive amount of previous necessary library work can be done at odd hours from home. Electronic books have made available the older literature, which in fact many of the books utilized in writing this textbook are on my smartphone as well as an iPad. One can literally be in touch with almost any older book, thanks to countless libraries that have scanned and put these treasures on the World Wide Web.

Information Technologies

So here we are, alive today at the dawn of the Information Age. What does it mean to have computers rapidly assimilating into the fabric of humanity? Twenty-three years ago the World Wide Web came into existence; prior to that all data had to be researched via classic book methods [26]. After Tim Berners-Lee's methods to incorporate hypertext into codes for computer manipulation, everything changed. The following table lists some of the firsts from this digital media capacity, and recall that in 1945 it was all predicted by Vannevar Bush [11].

Computer technology has followed Moore's Law with minor variation since Gordon Moore, cofounder of Intel, wrote of his observing the trends of microcircuits for the past 35 years. He actually stated that we could squeeze twice as many transistors on an integrated circuit every 24 months. The cost of that technology has almost halved in the same time period. In other words, the supercomputer of 1990 that cost $100,000 is today available in a $150 Nintendo system. Randall Tobias, former vice president of AT&T, is widely quoted as saying, "*if we had similar progress in the automotive industry, a Lexus would cost $2, it would travel at the speed of sound, and go 600 miles on a thimble full of gas*." In other words, things are accelerating with increasing rapidity [5].

Computational prowess started many years ago, and some would estimate that we have passed through more than 20 doublings on the exponential scale. In a more obvious sense, when the Internet came out of "nowhere" during the early 1980s, 20,000 nodes increased to 80,000 nodes within 2 years and no one noticed. But in the late 1990s when it went from 20 million to 80 million nodes, the impact has been dramatic. It has been anticipated that Moore's law should run out of physical possibility by 2019. But in retrospect, there have been other trends antecedent to Moore's observations that are also exponential. Moore's observations were based upon his observations on microchip manufacture. As one technology has ended its physical capacities in computational ability, another has arisen to take its place. Chips today are flat with no three-dimensional architecture, yet our brains massively parallel process in 3D. Computational models of the human brain are also rapidly expanding. The possibility of nearly limitless computational capacity also exists with quantum effects. Research in this area is rapidly progressing [24].

All of the other elements necessary for intelligent technology progression are also accelerating at exponential rates. Memory, for instance, which Moore did not include in his initial projections is advancing exponentially. The amount of memory utilized in the entire Apollo space program is readily available on a $150 game today. In fact, Oak Ridge's Titan supercomputer runs on processors that were originally developed for gaming. Exponential growth has been observed in communications technology as well. The technology of fiber optics, optical switching, electromagnetic transmissions, and others are all converging to make communications faster and faster. The power of wireless communication is also doubling every 10–11 months. The Tokyo Tech laboratory has recently set the record of wirelessly transferring data at 6.3 Gb/s. Do you think that the speed of light is the limit? How about recent observations at CERN regarding quantum locking? Apparently two elementary particles separated in a large accelerator can communicate with one another faster than the speed of light. The phenomenon has now been confirmed with larger particles as well [27]. A mechanism of "*instantaneous communication*" might therefore be possible.

As mentioned previously, Titan supercomputer is capable of calculations of 17.59 quadrillion calculations per second. The human brain is estimated conservatively to perform at 20 quadrillion calculations per second. Yet, electric circuits already are ten million times faster than the fastest neurons.

The ability of our computational machines to emulate our own biological processes is also being investigated. Ted Berger and colleagues at Hedco Neurosciences have devised integrated circuits that precisely match the digital and analog processing characteristics of neurons and clusters of neurons. One step further along is the group from Caltech that microprocessors that now emulate the digital-analog characteristics of mammalian neural circuits. Much work is ongoing in what is called "*chaotic computing*" which parallels the human brain's capability of processing patterns from the frenzied activity of entire networks of neural firing [28]. Eventually stable patterns emerge and a logical "*decision*" arises. All of this has been modeled mechanically. The question becomes: Is the human brain that much different from our mechanical computers?

Artificial Intelligence

Artificial intelligence (AI) uses computer technology to strive towards the goal of machine intelligence and considers implementation as the most important result; cybernetics uses epistemology (the limits to how we know what we know) to understand the constraints of any medium (technological, biological, or social) and considers powerful descriptions as the most important result. The computer chip comes from germanium or silicon solid-state transistors that were first of two Nobel Prizes in physics for John Bardeen (the only physicist to win two Nobel Prizes in physics) [29]. In 1950, ENIAC at the Moore School of Electrical Engineering at the University of Pennsylvania was the first modern electronic computer with the essential features found on current computers. By the early 1950s, microprocessors began to be conceptualized, and computers began to make their way into scientific and business accounting [30]. In the summer of 1956, John McCarthy who founded the Stanford Artificial Intelligence Laboratory (SAIL) along with Marvin Minsky (then at MIT), started a 6-week workshop at Dartmouth College on "*Artificial Intelligence*." There were 12 original participants in the prophetic group. The field of AI came into being when the concept of universal computation, the cultural view of the brain as a computer, and the availability of digital computing machines were combined [31]. The field of cybernetics came into being when concepts of information, feedback, and control were generalized from specific applications (i.e., in engineering) to systems in general, including systems of living organisms, abstract intelligent processes, and language. Already mentioned were Vannevar Bush's vital contributions with his view of the information revolution. Ted Nelson conceived and designed hypertext and the systems for storing and transferring information. Tim Berners-Lee followed by delivering the World Wide Web to his employers and built and placed it upon the nascent Internet of the early 1990s.

The exact beginning of cybernetics is perhaps difficult to ascertain, but the article "*An essay on the origins of cybernetics*" from a 1959 article by D.L. Stewart is the best place to start [32]. He notes that the word cybernetics was derived from the Greek kubernetes or *steersman* and was coined by Norbert Wiener a professor of mathematics at MIT. But like many things in history, everyone overlooked a little understood paper by James Clerk Maxwell from the Proceedings of the Royal Society of London in 1868 "*On Governors*" [33]. Wiener started meeting with other young scientists monthly at Vanderbilt Hall in the early 1940s. One of the first investigators he met was a Harvard Medical School professor of physiology Arturo Rosenblueth. This pair would later team up during the war years to investigate a machine's ability to predict voluntary control (desperately needed for wartime anti-aircraft design systems). By 1943 these investigations were published in the Philosophy of Science called "*Behavior, purpose and teleology*" [32]. They specifically defined behavior as any change of an entity with respect to its surroundings. This began the scientific understanding of mechanized actions or the understanding of human behavior with mechanized processes. Their first classification separated active behavior, in which the object is itself the source of energy in the output, and non-active behavior or passive behavior in which all the energy in the output comes from the immediate output. The essence of their theories was based upon feedback loops for control; the mathematics was just beginning at this time. They stated, "*the broad classes of behavior are the same in machines and in living organisms….while the behavioristic analysis of machines and living organisms is largely uniform, their functional study reveals deep differences*" [32]. Wiener and Rosenbleuth's ideas would begin to stimulate formal scientific investigation when the Josiah Macy Jr. Foundation organized a series of scientific meetings to fertilize new methods of investigation throughout the 1940s. By the 1950s the term "*cybernetics*" was increasingly utilized to describe much of the scientific investigation of control mechanisms, digital processing, and of course computer technologies and intelligent systems.

Artificial intelligence systems have been applied to medicine as neural networks. These networks were set up using self-organizing maps to become increasing powerful tools to evaluated complex data inputs and eliminating subjective basis of evaluation. The power of this method was clearly demonstrated when a computer beat the physicians in diagnosing meningitis in 1997. Now such artificial neural networks (ANNs) have been increasingly utilized in a wide and spectacular array of medical uses: diagnosis (echocardiography, brain mapping, lung scans, and prostate biopsy readings), therapy (gastroesophageal reflux algorithms), effect of treating (methadone in addiction), Alzheimer disease therapies, and modeling obesity outcomes [34]. But stone disease is also complex and such types of artificial intelligence is just beginning to be investigated, for instance, in the predictive possibility of ureteral stones passing with or without the aid of medications [35]. The promise for this technology in the care and management of patients with urolithiasis and perhaps in managing the literature itself has substantial promise for the use of ANNs [36].

Biotechnology

As physicians, the bottom line comes from the technologies that directly impact upon the way we practice medicine. Biotechnologies are dominated by those processes that the news media hypes, the headliners. The two most dominant headline biotechnologies recently are the Human Genome Project and cloning. The technology behind the Human Genome Project was DNA sequencing. About 15 years ago, when DNA sequencing was in its infancy, it was estimated that it would take thousands of years to sequence every base pair on the whole of human chromosomes. But the entire sequence was completed in just under 15 years at a cost of several millions of dollars. In fact, you can now purchase your very own DNA sequencer and perform this amazing feet of biotechnology yourself at home. Another example would be the 15 years it took to sequence the human immunodeficiency virus

Table 32.1 DNA sequencing costs through the Human Genome Project till the current time [37]

Date	Cost per Mb of DNA sequence	Cost per genome
September 2001	$5,292.39	$95,263,072
March 2002	$3,898.64	$70,175,437
September 2002	$3,413.80	$61,448,422
March 2003	$2,986.20	$53,751,684
October 2003	$2,230.98	$40,157,554
January 2004	$1,598.91	$28,780,376
April 2004	$1,135.70	$20,442,576
July 2004	$1,107.46	$19,934,346
October 2004	$1,028.85	$18,519,312
January 2005	$974.16	$17,534,970
April 2005	$897.76	$16,159,699
July 2005	$898.90	$16,180,224
October 2005	$766.73	$13,801,124
January 2006	$699.20	$12,585,659
April 2006	$651.81	$11,732,535
July 2006	$636.41	$11,455,315
October 2006	$581.92	$10,474,556
January 2007	$522.71	$9,408,739
April 2007	$502.61	$9,047,003
July 2007	$495.96	$8,927,342
October 2007	$397.09	$7,147,571
January 2008	$102.13	$3,063,820
April 2008	$15.03	$1,352,982
July 2008	$8.36	$752,080
October 2008	$3.81	$342,502
January 2009	$2.59	$232,735
April 2009	$1.72	$154,714
July 2009	$1.20	$108,065
October 2009	$0.78	$70,333
January 2010	$0.52	$46,774
April 2010	$0.35	$31,512
July 2010	$0.35	$31,125
October 2010	$0.32	$29,092
January 2011	$0.23	$20,963
April 2011	$0.19	$16,712
July 2011	$0.12	$10,497
January 2012 (EST)	$0.09	$7,950

(HIV) but only 31 days to unravel the SARS virus. Sequencing is following the same exponential technologic growth pathway that applies to computers, intelligent technologies, and everything else we've used as examples (Table 32.1) [37]. Biotechnology-based gene therapies are in their infancy, but already there have been an estimated 350 spin-off products from the fruits of the Human Genome Project [38].

Genetic manipulation itself is going to be the next major target of our advancing technologies. It is currently estimated that about 99 % of the drugs we use in medicine are found by the laborious pathways of classic drug development, manipulate one molecule and "*see what happens.*" Discovered in 1998, RNA interference (RNAi) is a normal biologic process that is used to regulate gene expression. Genetic technologies offer the potential for such things as RNA interference [39]. By blocking the fat insulin receptor in rats, they ate ravenously but remained lean. They did not develop diabetes, did not develop heart disease, and lived 20–25 % longer than non-blocked controls [40]. There are genes that control every aspect of our biological lives that are now open for pharmaceutical investigations. Complex genetic mechanisms associated with urolithiasis that we discussed in the chapter on Modern Science are beckoning to be turned off or suppressed. If the law of accelerating returns applies, and there is no reason to think that this industry will be immune, in 10–15 years mature gene therapies will be rapidly advancing in medicine. That folks is just one generation away!

Cloning is the next "headliner." Though manipulation of the human genome in this fashion may have already occurred, it is likely that other converging technologies might reduce the necessity to even pursue this capability. There are companies that are already synthesizing nanofactories to make chromosomes. They have been photographed and show some capacity of functioning in biologic systems. It is possible that with the maturation of biotechnology, we might be able to dramatically alter major diseases such as atherosclerosis and malignancy which we've struggled against for centuries. The next frontier will be aging itself, but lest you think this has not achieved significant scientific and technologic interest, you would be quite wrong. Just 1,000 years ago, human life expectancy was about 23 years. By the beginning of the Industrial Revolution in England (200 years ago), it was 37. By the completion of this same revolution, again in England in 1900, it was 50 years. Currently, it is estimated to be about

79.2 years and rising [41]. What is the ultimate limit of human existence? No one actually knows, but we do know that some organisms do seem to be immortal. The genetic mechanisms that control for this phenomenon are only now just becoming unraveled. The genetic aspects of stone manipulation should be child's play compared to human life prolongation.

Nanotechnology

The Nobel Prize physicist Richard Feynman predicted in a 1959 talk entitled "*There's plenty of room at the bottom*" that there was the theoretical possibility of manipulating things on a molecular scale [13]. Prior to this prophetic lecture, Albert Einstein as part of his doctoral dissertation (1905) calculated that the size of a single sugar molecule was about a nanometer in diameter (for scale imagine that ten hydrogen atoms side by side, it is one thousandth the length of a typical bacterium, one millionth the size of a pinhead) [42]. The first living cells housing nanoscale biomachines evolved 3.5 billion years ago. In 400 BC Democritus coined the word "atom," thought to be the basis of all matter. In 1931 Max Knoll and Ernst Ruska developed the electron microscope for subnanometer imaging. In 1959 Richard Feynman gave the prophetic lecture predicting the rise of nanotechnologies. In 1968 Alfred Y. Cho and John Arthur of Bell labs invented molecular-beam epitaxy to deposit single atomic layers on a surface. In 1974 Norio Taniguchi conceived the word "nanotechnology." In 1981 Gerd Binnig and Heinrich Rohrer created a scanning tunneling microscope, which can image individual atoms [5]. By 1985 Robert F. Curl, Jr., Harold W. Kroto, and Richard E. Smalley discovered buckminsterfullerenes, also known as buckyballs, which measure about 1 nm in diameter (1996 Nobel Prize) [43]. These are 12 carbon compounds that are made from the vapors of carbon dust and form very structurally sound covalent bonds. The carbon buckminsterfullerenes provide almost 1,000 times the strength of steel and have the capacity to auto-organize themselves if damaged. They might also represent a unique delivery system of encapsulated genetic material to manipulate genetic defects.

D. Eric Drexler published his futuristic book Engines of Creation in 1986 that popularized nanotechnology. In 1989, Donald M. Eigler of IBM wrote the company's name using individual xenon atoms. In 1991, Sumio Iijima of NEC in Tsukuba, Japan, discovered nanotubes (again described in lay terms). In 1993, Warren Robinett of the University of North Carolina and R. Stanley Williams of the University of Southern California at Los Angeles devised a virtual-reality system connected to a scanning tunneling microscope that lets the user see and touch atoms. In 1998 Cees Dekker's group at the Delft University of Technology created a transistor from a carbon nanotube. In 1999, James M. Tour at Rice University and Mark A. Reed of Yale University demonstrated that single molecules can act as molecular switches. In 2000 the Clinton administration announced the National Nanotechnology Initiative, which provided a big boost in funding to nanoresearch. Later in that same year, Eigler and others devised a quantum mirage with a magnetic atom, proving a possible means of transmitting information without wires at a molecular level [5].

Currently there are several proposals to the National Nanotechnology Initiative for medical applications. Some are for diagnostic possibilities including the use of artificial magnetic crystals that detect particular biologic entities such as pathogens. Other applications include the use of semiconductor nanocrystals, a quantum "dot." These dots owe their special properties to quantum mechanics and emit photons of light in only one specific wavelength. These quantum "*dots*" can be attached to DNA sequences which when scanned can act like a genetic bar code, looking for flaws. A dendrimer is a branching molecule roughly the size of a protein that has a large internal surface area. They can be created in a variety of sizes and might be able to transmit DNA sequences into cell's nuclei much safer than virus particles [44]. Other dendrimers might be able to act as micro-drug delivery vectors. Nanoshells are small beads of glass coated with gold that can absorb light, particularly near-infrared, which can be beamed into the body. These nanoshells could then be induced from an extracorporeal strong infrared source to be heated. Buckyballs can be made from just a few dozen carbon atoms. The potential for the future of nanotechnology like many other futuristic applications to medicine is unknown. But it is intriguing to speculate about the possibilities. Using artificial scaffolds that nanotechnology might conceive, cancerous tumors at the cellular range might be identifiable and destroyed. Using synthetic scaffolds, we might be able to regenerate bones, cartilage, skin, or more complex organs such as diseased kidneys.

To Err Is Human

> "*Too much of the public- and certainly to lawyers and the media- medical error is fundamentally a problem of bad doctors. The way that things go wrong in medicine is normally unseen and, consequently, often misunderstood. Mistakes do happen. We tend to think of them as aberrant. They are, however, anything but*." [1]
>
> Atul Gwande

Kohn and colleagues have estimated that between 44,000 and 98,000 deaths annually have been attributed to medical error in their work *To Err Is Human* [45]. As the rise of stone surgery is almost entirely dependent upon the technology and skill of the surgeon, there has been increased emphasis on comparing the surgeon to the airline pilot. In aviation, the pilot is expected to perform with a risk of failure less than 0.0001 %. Complications in surgery occur in the range of 1–5 % or more, this is a factor of 100× more than in the airline industry. Many operative modifications have been instituted to control preventable errors in the operating room, but truthfully not many of these actually apply to stone patients. For instance, wrong site errors are not even a realistic probability in patients with stones; though patients can present with bilateral stones, there are no real reported cases of this phenomenon. The errors in stone disease management can come from lack of skill; a surgeon, for instance, elects to perform one procedure when another is likely to benefit the patient preferentially, or unexpected anatomical variation makes an approach risky. The most common scenario is a large renal stone that might best be managed with a percutaneous nephrostomy and an antegrade nephroscopic approach that the surgeon may not be comfortable performing. All too often, a shock wave lithotripsy is chosen because sadly the reimbursement level is higher than some more applicable method. Our system of reimbursement in the United States has evolved into a nightmare of complexity and one that no longer reflects upon reality [46]. These financial disincentives have to be considered in a realistic discussion of error and more often than not are disregarded or relegated to the backroom discussion [47]. Atul Gwande mentions the notion of professionalism that would normally be considered the check to such unprofessional behavior. He states, "*All learned occupations have a definition of professionalism, a code of conduct. It is where they spell out their ideals and duties. The codes are sometimes stated, sometimes just understood. But they all have at least three common elements. First is an expectation of selflessness…second is an expectation of skill…third is an expectation of trustworthiness*" [48]. These are truly great expectations for rules of professionalism in an era of spending cutbacks, limitations in hours, financial cliffs, and rising malpractice costs. But a patient is on the other end of this professionalism equation and that can never be forgotten.

"*Through all of human history, health caregivers have been respected individuals in society. Now with the Internet, consumerism, the Baby Boomers aging, risk adjustment, outcomes measurement, and quality metrics, blind trust in clinicians has begun to erode*" [49]. It is hard to find confidence in a system that appears to be spiraling out of control. Two sentinel studies that were used by the Institute of Medicine to generate their pronouncements in *To Err Is Human* came from the 1991 *Results of the Harvard Medical Practice Study I & II* [50, 51]. The first study was a retrospective review of 30,121 randomly selected records from 51 randomly selected places in New York State in 1984. They found adverse events in 3.7 % of these hospitalizations and 27.6 % of these were secondary to negligence. They found that 70.5 % of these errors resulted in disability that persisted for less than 6 months, 2.6 % resulted in permanent disability, and 13.6 % led to the patient's death [50]. Their second piece immediately followed looking at the nature of these errors. Drug complications were the most common adverse event (19 %), wound infections in 14 %, and technical complications in 13 %. The major area that was isolated was diagnostic errors in 75 % and what were called "*noninvasive therapeutic mishaps*" or errors of omission (77 %) [51]. The other major study utilized by the Institute of Medicine was *Costs of Medical Injuries in Utah and Colorado* published in 1999 [52]. This also was a largely Harvard School of Public Health endeavor. In this evaluation they identified 459 adverse events, of which 265 were preventable from 14,732 randomly selected discharges from 28 hospitals. The costs associated with adverse events equaled $348,081,000 and about ½ of that number from the preventable errors [52]. Clearly the technologies that we have presented could solve many, if not most, of these errors as time goes on and the cost savings in error prevention would pay for the technology. The professionalism of those involved was not evaluated, nor is there a method to evaluate this quality of the health caregivers. The Institute of Medicine followed their first publication with recommendations for fixing the trouble US healthcare system with a second, *Crossing the Quality Chasm* [53]. In this volume they begin with "*The American health delivery system is in need of fundamental change. Many patients, doctors, nurses, and health care leaders are concerned that the care delivered is not, essentially, the care we should receive*." In nine chapters they proceed to relate how they think that a new and improved health system can be created.

How does all of this apply to the history of urolithiasis and what are the implications to the treatment of stone disease? In a related paper in the Journal of Urology in 2001, a survey of urologic medical malpractice cases was reported. They were able to identify 259 medical malpractice claims from 1995 to 1999. The average urologist gets sued for malpractice twice in his career and certain parts of the country were worse than others (Southeastern > North Central > South Central > New England > Mid-Atlantic > Western > New York) [54]. They also noted that the most common procedure-specific claim was for endoscopic procedures (22 %) with most being stone patients. In another study involving malpractice litigation in one state, New York, 469 urologic claims occurred between 1985 and 2004 with a remarkably constant 22 claims annually during this period. Claims based on endourologic procedures (mostly stones) were the second leading cause of malpractice claims in NYS, second only to oncologic operations (25 vs. 46) [55]. In a follow-up on this same group of malpractice claims, missed diagnosis led to malpractice claims in 75 cases, and only two of these were stone related, both kidney stones [56]. Now getting to the stone group and a different group of investigators but still looking at New York State from 2005 to 2010, we can gather even better information. There were 25/585 closed claims that were related to endourology (4.3 %). Sixteen of these cases were women and nine were men. Twenty-two of these cases involved stones; the remaining three were from ureteral obstruction. Cystoscopy and stent placement accounted for most of the suits (52 %) followed by ureteroscopic lithotripsy (32 %), shock wave lithotripsy (8 %), and percutaneous procedures (8 %). Sixteen patients (62 %) required secondary procedures following their complications and six (24 %) died, all from sepsis. Ureteral stones were the major culprits in about 80 % of these cases [57]. Things go wrong far more commonly than medical malpractice cases get filed in our tort system. With the emphasis on the historical perspective, in fact, things go wrong a lot less commonly now than at any previous time in surgical history. Yet our stone patients are still dying on our watch; complications are still occurring with some degree of regularity. Though communication with the patient and the family has been widely proclaimed along with excellent documentation to help minimize the threat of the lawsuit, what about preventing the errors that result in injury of unintended outcomes to begin with?

Six Sigma

> "*In health care, building a safer system means designing processes of care to ensure that patients are safe from accidental injury.*" [45]
>
> —To Err Is Human

The abilities of our truly spectacular explosion of knowledge and technology need to come home to roost at some point, and that point is to prevent further error. This is the point of this exercise in future aggrandizement from a historical perspective. We are everyday surrounded by the living palimpsest of our species historical fight against urolithiasis yet we blithely continue often oblivious to the sacrifices of the past on our headlong journey to the future. I would like to quote Gwande once more, not because he is a urologist's son:

> "*Here, then is our situation at the start of the twenty-first century: we have accumulated stupendous know-how. We have put it in the hands of some of the most highly trained, highly skilled, and hard working people in our society. And, with it, they have indeed accomplished extraordinary things. Nonetheless, that know-how is often unmanageable. Avoidable failures are common and persistent, not to mention demoralizing and frustrating, across many fields- from medicine to finance, business to government. And the reason is increasingly evident. The volume and complexity of what we know has exceeded our individual ability to deliver its benefits correctly, safely, or reliably. Knowledge has both saved us and burdened us.*" [48]

Let us look as an example of a worrisome problem in stone disease, looming large on the horizon and that is the increasing prevalence of predominately calcium phosphate stone formation. In the past two decades an increase in calcium phosphate stones has been noted in the United States, with females being more common than males [58]. We have seen that brushite stone formation is often concurrent with apatite plugging of the papillary tubules leading to fibrosis and permanent renal injury. This is becoming an increasingly disconcerting trend in urolithiasis and should serve as a warning to those of us who see and treat many recurrent stone formers to be ever vigilant to this possible conversion to a worse scenario [59]. In addition, it appears that our interventions in stone formers by repeated shock wave lithotripsy in particular might indeed be damaging the kidney itself and also contributing to the transformation from calcium oxalate stones to calcium phosphate stones [60].

One might also argue that the advance in shock wave lithotripsy itself has not actually advanced, that, in fact, the methods and results have gotten worse. But our abilities to gauge success have improved, and CT scanning post-treatment is much better on finding pieces of stone than was the KUB. One thing is certain: if a shock wave lithotripsy fails to break up the stone, odds are given our current technologies that another method should be utilized in subsequent interventions. Multiple, serial shock wave lithotripsies should not be considered the method of choice for dealing with non-fragmentable stones [61]. In addition, in skilled hands the holmium:YAG (yttrium-aluminum-garnet) mid-infrared laser remains currently unsurpassed and the most effective lithotripter source in the surgical armamentarium in the urologist's arsenal. With ureteroscopes evolving into smaller and improved optical capacity, there are virtually no regions within the kidney or ureter that can avoid these diminutive scopes' abilities. But complications can and do occur, but with systems in place to carefully monitor performance and follow-up of patients, one could speculate that Six Sigma (or 1/million) might not be achievable soon, but the aviation standard of 1/10,000 just might. Anesthesia using Six Sigma tools has now dropped its serious complication rate down or "*mishaps*" to near 1/200,000 [62]. Let us focus our attention on this amazing and truly underappreciated bit of fact. Ellison Pierce was fixated on the notion that unacceptable numbers of serious complications occurred in anesthesia and when he was elected to be vice president of the American Society of Anesthesiology in 1982 he had opportunity to do something about it. He recruited an engineer named Jeffrey Cooper who utilized a technique referred to as "*critical incident analysis*" to begin a systematic approach to all aspects of the anesthesia/patient interaction [63].

The first in-depth analysis of 359 errors broke the whole process of anesthesia down in sections which were then attacked by solving or developing solutions to problems—utilizing pulse oximeters, placing end-tidal CO_2 monitors on anesthesia machines, and standardization of anesthesia machines and even the dials on the gas cylinders [63]. Others are just beginning to follow this pathway, but with the evolution of technology occurring as it is by quantum leaps, why should stone disease management have to wait much longer?

The Future of Stones

Technology and microelectronics are revolutionizing every aspect of our society. Polymer science, microcomputerization, optical engineering, bioengineering, and many other technologic arenas are being focused upon advanced healthcare delivery. Surgery has not been immune to such technologic advancement. The precise extent and overall impact of new, minimal access urologic surgeries has almost certainly not yet achieved its limits. This logarithmic growth in minimally invasive stone procedures reflects both the clinician's abilities to adapt to new technology and also the patient's themselves desiring centers where such methods are being utilized. With the rapid dissemination of knowledge by mass media, an ever increasingly informed society is seeking alternative therapy for heretofore conventional open operations. Minimal access surgery is a redefinition of the term for technologically advanced surgery originally coined by J.E.A. Wickham in 1987, referred to as the "*new surgery or minimally invasive surgery*." [64] These terms are just a method of quantifying the degree of surgical trauma inflicted upon patients. Laparoscopic surgery has been correctly pointed out by Cuschieri to produce minimal access trauma but still imparts surgical trauma. Minimal invasive surgery is the next echelon vis-à-vis further reduction of risk and trauma for patients [65]. This type of surgery does minimize trauma by eliminating direct organ dissection and cutting through the bodies walls via "classic" methods. Endoscopic surgeries next reduce the trauma by proceeding through natural orifices to gain access to the stones (in our focused case) in the urinary tract. Shock wave lithotripsy eliminates any invasion through the body or via any natural orifices and utilizes high-energy shock waves to comminute the calculus. But one might correctly assume that this technologic advance is not quite finished and that newer, safer alternatives might yet be invented.

Surgical progress has been a series of "quantum leaps" based upon technological advances. Wickham identifies five eras of surgery based upon these technologic advances: preanesthetic era, postanesthetic era, the era of supportive medicine, the era of conservative surgery, and the era of minimally invasive surgery [66]. Each era is characteristically diminishing in the timed constraints for progression to successive levels or the law of accelerating returns applied to surgery. Now robotic surgery has begun to replace the methods that were being discussed by Wickham and it has been less than a decade. The robotic systems will certainly evolved and have great potential. Perhaps the "*human factor*" of error can be programmed out of these robotic systems [67].

Urologists, more than any other surgical specialty, should be aware of the patients' demand for alternative therapies. In the earliest surgical days of perineal lithotomy, mortality was age dependent and greater than 50 % of the patients died and probably many more suffered irreversible harm. Cheselden with his scrupulous separation of "observed" cases from his private practice (unobserved cases) reported statistics only on the former. Even with the development of transurethral lithotrity, there was an impressive mortality. Patients and surgeons were inured with death, suffering, and morbidity. We fortunately have evolved beyond this pain and suffering with great expectation to advance even further. Most of us have lived through two revolutionary eras of urologic practice: the endoscopic treatment of prostatic disease and the abdication of open stone surgery. Wickham has chosen the latter to represent the traumas inflicted upon our patients and the result of technology on reducing them. Progressing from open stone surgery through percutaneous nephrostolithotripsy and including first- and second-generation shock wave lithotripsy therapy, patients are subject to less and less interventional trauma [68]. The results are dramatically reduced hospital stays, faster return to normal activities, and patients who are very aware of their good fortune. In one decade, urologists have progressed in the treatment of stone disease further than any other surgical specialty though this too is changing.

Discussion

> "*It is difficult to accept recurrent stone formation as incidental in any patient and allow it to continue without efforts to understand its causes and offer such treatments as seem appropriate*." [69]
>
> —Frederic Coe (2005)

Morbidity and mortality conferences, called M&M, began in hospitals and the practice of medicine early in the twentieth century. By 1901 a standardized method of case reporting had been developed at Johns Hopkins Medical School. This was an attempt by early health professionals, physicians, and nurses to investigate the outcomes of care (Osler with the blackboard). This became mandated in the United States by the Accreditation Council for Graduate Medical Education in 1983. Unexpended findings at autopsy also were historically significant in evaluating the cause of death. Lundberg noted 40 % discrepancy between antemortem and postmortem diagnoses in 1998 [70]. Autopsies have continuously declined throughout the twentieth century. In the 1940s autopsy rates were typically at 50 %, but currently they are performed in less than 9 % of hospital deaths. Stone disease no longer has the high mortality rates that were ascribed to the past, but they still rarely occur. It is the morbidity that is frequently associated with stone disease presently that is of concern and the rising rates of prevalence of this disease. The *perfect storm* situation that underscores the concern for this morbidity is the overuse of shock wave lithotripsy in some regions for kidney stones, possibly because the reimbursement for this modality is so much higher than equally or in some cases more effective therapies [46]. When reimbursement begins to have a factor in the decision for therapy, there are all kinds of ethical concerns that come into play, outcomes typically not being foremost in consideration. Our hope for the future of technology is that it will solve this dilemma as well as make safer, less invasive methods readily available to urolithiasis sufferers.

"*The integration and synergy of the four technologies (nano-bio-info-cogno) originate from the nanoscale, where the building blocks of matter are established. This picture symbolizes the confluence of technologies that now offers the promise of improving human lives in many ways, and the realignment of traditional disciplinary boundaries that will be needed to realize this potential. New and more direct pathways towards human goals are envisioned in working habits, in economic activity, and in the humanities*" [16]—thus begins the first National Science Foundation/Department of Commerce-sponsored scientific meeting on technologic convergence on June 2002 in Arlington, Virginia. Called "*Converging Technologies for Improving Human Performance*," this government-sponsored conference covered all aspects of rapidly expanding technologies [16]. We have spent a good bit of this chapter discussing the exponential growth of divergent technologies—nano, bio, info, and cogno. What happens when they start to blur and combine to achieve the same ends? This is indeed what is happening. The old constraints of specialization are being wiped out by the supercomputing systems currently being implemented. Computers are becoming so powerful and fast that autoengineering systems are not only capable; they are the only method that can create the computer chips that are being used by the computers. This technology is crossing over to other design systems, engineering, and research and development. In other words, as intelligent technologies rapidly become more intelligent, the pace of change is further accelerated. The technology that will be with us tomorrow is definitely not with us currently. As with buying a computer currently, you can wait until the next bigger, faster, more sophisticated system becomes available and you will end up waiting forever. Or, you can scratch your head and get into the technology and become inspired to seek and discover all you can that the technology can offer. Welcome to the Information Age, where "business as usual" simply does not apply.

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33 Epilogue

"In the life of a man, his time is but a moment, his being an incessant flux, his senses dim rushlight, his body a prey of worms, his soul an unquiet eddy, his fortune dark, and his fame doubtful. In short, all that is of the body is a coursing waters, all that is of the soul as dreams and vapours; life a warfare, a brief sojourning in an alien land; and after repute, oblivion. Where then, can man find the power to guide and guard his steps? In one thing and one alone: the love of knowledge." [1]

—Marcus Aurelius, *Meditations*

On Epilogues

The appendix or supplement to any written work is typically called an epilogue; however, the great dramaticists of plays also used epilogue to frame a completed work. The term naturally arises from Greek mythology in the saga of the two Titan brothers, Prometheus and Epimetheus. Prometheus is remembered for stealing Zeus's fire and giving it as a gift to humans. Epimetheus is remembered in delivering punishment to humans for accepting this gift by providing Pandora her infamous box (more on this a little later) [2]. So literally speaking, prologue is forethought, and epilogue is afterthought in literary writing. Classically, William Shakespeare comes to mind for his use of prologues; for instance, in *A Midsummer Night's Dream* he apologizes for his play in a wily way in order to promote a sense of good humor prior to beginning the play. His friend and fellow playwright Ben Jonson chose the epilogue as his venue for further putting intentions to his audience [3].

One is expected to write the supplement of a literary work in the dramatic fashion that the work engenders. This is a book about the history of urolithiasis. Lithotomy was perceived to be a barbaric period of urologic history enshrouded by the great Hippocratic Oath specifying that this should only be done by those adept in this art. Many papers in the history of surgery deal with this phrase of the oath by suggesting that urologists, those who deal with urinary tract diseases, were identified early in medicine as unique [4–12]. That is probably, like much of history, not quite the whole truth but merely a historian's representation of their particular view of the truth. People often look at history with a revisionists perspective and alter whatever that is easily alterable to the modern purpose. This is a revisionist's history. The Hippocratic Oath has no real ancient legacy. The known first allusion to the Oath is from a Latin physician by the name of Scribonius Largus. He wrote about the duties of physicians in his text entitled *Compositiones* [10]. Scribonius appears to believe that the taking of an oath is simply part of being in the medical profession. He appears to expect that physicians have taken an oath,

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and he bases his understanding of the core principles of the profession to be mercy and humanity [10]. The particular oath is not really specified though.

On History

Our modern Western thought is inexplicably linked to ancient Greek civilization and thought [13]. Greek mythology represents some of the earliest writings that have been preserved as were the folktales written by Homer. One needs look no further to the implications of health and disease upon society than the myths recounted by the Ancients and the events surrounding the Greek gods. Hephaestus was the Greek god of fire, but particularly the blacksmith's fire, as he would become the patron of craftsmen, artisans, and manufacturers [14]. He was depicted in ancient works of sculpture and paintings as the lame god, born from Hera who despised him because of his weak and crippled form. As the story goes, he is cast out of Mount Olympus by the repulsed Hera and falls for an entire day before landing in the sea. He is rescued by nymphs who carry him to the island of Lemnos where he builds a palace and his forges under a volcano. Hephaestus creates a golden throne as a present to Hera, but his intentions are sinister and she becomes entrapped. Dionysus is sent by Zeus to intoxicate and bring Hephaestus back to Mount Olympus in order to entreat him to release his mother. This is of course attended to with a bribe, and Aphrodite is promised to Hephaestus as his wife [14].

Hephaestus was the great craftsman for the gods and supposedly created many wonderful devices out of metal. His primary helpers were the Cyclopes, who assisted him as workmen. He made weapons and armor for the gods and their heroes. He made Athena's shield and Aros' arrows. He manufactured the chariot for the sun god, Helios, and the invincible armor for Achilles. In the Greek creation myth, it is Hephaestus who is given the ingenuity of creating the female gender by shaping Pandora (meaning, "all gifts") out of clay. It is also Hephaestus who is ordered by Zeus to chain Prometheus to the rock in Mount Caucasus [14]: "*Against my will, no less than yours, I must rivet you with brazen bonds… Such is the prize you have gained for your championship of man*" [15]. In addition, some of Hephaestus's other creations included an animated bull given to King Aeetes that could breathe fire from its mouth. He wrought the famed necklace of Harmonia and Oengrioun's fabulous underground house [14]. But it is the Pandora myth that calls our attention, perhaps for two reasons. First, it is the gift and what is inside that has some relevance to this historical sojourn. And, second, there is the historical misconception of Pandora's box that is allegorical to our understanding of history.

So as the myth goes, Prometheus steals Zeus's fire and brings it as a gift to man. Prometheus was punished by being chained to Mount Caucasus where each evening his liver was devoured by Zeus's pet eagle. Hephaestus was to make a gift for the first woman, Pandora [14]. In this box is to be placed all of the afflictions that will forever plague mankind: disease (particularly urolithiasis), plagues, pestilence, and so forth. But the last thing in Pandora's little gift is hope, the vilest of all gifts because after all of the suffering of mortals, to end up with hope just keeps the insipid humans coming back for more. Now let's turn to the second peculiar thing about the Pandora myth. The word "box" was an error originally perpetrated by the Renaissance scholar and stone sufferer, Erasmus of Rotterdam, in an error he made translating Hesiod (pithos for pyxis). The actual (though mythical) container given to Pandora was in fact an amphora or bottle. So Pandora's box never really existed (really) but was always Pandora's bottle but hope is still the last gift (or curse) of the gods to humans [16].

On the History of Urolithiasis

"*Dum spiro, spero. While I breathe, I hope.*"

—Latin Proverb

It is worthwhile therefore to consider in such detail the convoluted history of urolithiasis for the purpose of setting forth, with some degree of completeness, the antecedent knowledge upon which modern science of stone disease rests, an edifice. To fully appreciate the legacy of those former sufferers, healers, quacks, barbers, surgeons, and philosophers that have extended us to the hope of true understanding of this truly ancient disease has been our goal. Also, history makes us appreciate the legacy of those who have tried so hard to lead us upon the true path of knowledge or epistemology. There is one final historical story that should be told to conclude this textbook. We have presented the works of Samuel Shattock and have presented in some detail his study of the ancient bladder stone of a predynastic Egyptian youth. This stone has been used by so many authors of papers and book chapters as an introduction to brief overviews of the history of urolithiasis that the stone itself should be considered a world treasure. It was studied minutely and the paper of Shattock is certainly a classic. He famously described the two oldest reported stones in humans in a 1905 paper entitled *An Egyptian Calculus. A prehistoric or predynastic Egyptian calculus* [17]. Like so much of ancient history, man's inhumanity to man intervened, and the museum holding this pelvis and stone was hit by an unintended bomb during the Battle of London in 1941. The stone had been unearthed by Professor G. Elliot Smith in 1901 and was destroyed in 1941, a good run though it was never truly the highlight of the Royal College of Surgeons museum that it should have been. The mummy and the stone were both destroyed. No parts were recovered and the tragic loss of this iconic monument of urolithiasis history has been lost forever.

Alexander Randall used the phrase "*no stone unturned*" in one of his early works on urolithiasis, and it easily could be utilized as a subtitle to this textbook on the history of urolithiasis. One final Randall fact is also worth presenting, he used the same paragraph twice in two papers a year apart, suggesting that they truly emphasized the character of his observations and they should be presented here [18, 19]:

> "*One cannot dwell upon the origin of primary renal calculus without, sooner or later, forming a firm conviction that there has to be an initiating lesion. Everything points toward it every known fact strongly suggests it, every pertinent question demands it, and pathology itself is incomplete without it! Stone is a symptom, and not a disease entity. Stone is made from the common salts in the urine. These salts exist in a supersaturated state. Stone will grow on any foreign tissue or foreign body. Stone has got to be a gradual accretion of crystals demanding a nidus for the seeding of such crystallization. Stone requires time to grow and, therefore, must be stationary and fixed in its beginning in order to gain clinical size.*" [19]

This complete history of urolithiasis followed a semi-acceptable method utilized by historians of chronology; however the author has taken great liberties by using his own agenda to present the historical aspects of urolithiasis that were felt to tell the story with some sense of a tapestry, weaving the fragments like a thread through the timelines of history. Though every effort was extended to provide detail and using primary references, the author fully submits his inability to read French and ancient Greek, his limitations on Latin, and profound regrets at having at times to not use some books, writings, and articles that are significant but felt to not add the necessary information to warrant their inclusion. The overarching personal agenda of the author has always been to combine art and science in a historical milieu so as to make R.G. Collingwood (from the first chapter) proud [20]. History is both an art and a science that is subject to the considerable spin by the historian. This is readily apparent let's say in the history of Abraham Lincoln that has become a nationwide fixation in recent years [21]. But the author of this history's agenda was not necessarily rewriting historical perspective, not fame nor glory, but simply to find and enjoy the depth of passion that the past brought to the understanding or urolithiasis. If we have captured some past moments that have brought some entertainment to the reader, then the art of the historical treatise has been achieved. If also we have spotlighted some forgotten soul or moment of stone lore that has slipped from collective memory and may augment some researchers reckoning of the timeline of epistemology, then the science aspect of the history has likewise earned its worth. It would be fitting to close with an Oslerism if at all possible, but first a note from Dr. Gibson's autopsy's notes [22]:

Kidneys

> *Left: slightly smaller than normal. On section the cortex which is injected is not diminished. A small ischaemic patch is seen on the outer border and slight arteriosclerotic atrophy towards the lower pole. The capsule strips easily leaving a smooth uniformly granular surface with the exception of a few depressions from ateriosclerotic atrophy.*

Right: About normal in size. On section paler than the left. The calices are slightly dilated and arteriosclerotic atrophy shows slightly. Scattered evenly in the cortex are pinpoint, buff-colored uratic deposits. The capsule strips readily leaving a smooth granular surface." [22]

Sir William Osler died on the afternoon of December 29, 1919, of bronchopulmonary infections and an empyema. His health through much of his 70-year life was excellent except for the recurrent bouts of ureteral colic which we have discussed previously. He had asked his friend and personal physician Dr. Gibson to perform an autopsy on him following his death [22]. So Osler died with the seeds of stone disease ever present in his right kidney, beckoning the ultrastructural morphology of Andy Evans to further our knowledge. But let's end this tome with a beginnings of sorts that was Osler's most memorable piece for the graduating class of the University of Pennsylvania on May 1, 1889 [23]:

"*To many the frost of custom has made even these imposing annual ceremonies cold and lifeless. To you, at least of those present, they should have the solemnity of an ordinance- called as you are this day to a high dignity and to so weighty an office and charge. You have chosen your Genius, have passed beneath the Throne of Necessity, and with the voices of the fatal sisters still in your ears, will soon enter the plain of Forgetfulness and drink of the waters of its river. Ere you are driven all manner of ways, like the souls in the tale of Er the Pamphylian, it is my duty to say a few words of encouragement and to bid you, in the name of the Faculty, God-speed on your journey.*"

—William Osler, Aequanimitas, 1889 [23]

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