JOURNAL OF ENDOUROLOGY
Volume 19, Number 10, December 2005

Epochs in Endourology

Sir William Osler's Perceptions of Urolithiasis and the Case of the Indigo Calculus*

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ABSTRACT

***Background*: Sir William Osler published his textbook, *The Principles and Practice of Medicine*, in 1892. It became the definitive treatise on a wide variety of diseases. The section on nephrolithiasis clearly presents the etiology, pathology, symptoms, diagnosis, and treatments. What remains a mystery is the mention, under rare forms of human stones, of a type called "indigo."**

***Materials and Methods*: A search of *Index Medicus* starting from 1909 backward to its inception in 1879 was performed for key words "indigo," "calculus," "renal" or "bladder stones" and "indicanuria." Twelve textbooks of urology published before 1940 were scrutinized for references to indigo calculi.**

***Results*: Only two references to indigo were found, both related to its use for treating constipation (1887 and 1891). Of the 12 textbooks, only 4 make passing reference to "indigo stones." They all mention that such calculi are very rare, but direct references to cases are lacking. One textbook references a study of blue stones from Egyptian mummies.**

***Conclusion*: It is unlikely that Osler's reference to an indigo calculus was taken lightly during his writing of *The Principles and Practice of Medicine*. The case of the indigo calculus is fascinating and perhaps enlightening if only for the source of Osler's intrigue.**

INTRODUCTION

SIR WILLIAM OSLER, although Canadian, is known as the father of modern American medical education and was Professor of Medicine at Johns Hopkins University (1890–1905). He published the standard medical textbooks for the beginning of the 20th Century, *The Principles and Practice of Medicine*. Osler was widely regarded as the physicians' 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.[1] His perceptions of a wide variety of medical disease processes reflect his extensive background in pathology and a uniquely inquisitive temperament.

In the first edition of the *Principles*, Osler clearly identifies a rare type of stone afflicting humans as "indigo."[2] Very little information was given, and little to no modern literature exists to substantiate his claim. Several questions arise in this regard, particularly where does this organic pigment fit into urinary stone disease? There is no modern mention of indigo in kidney stones from the 1940s onward. Calls to North American stone-analysis laboratories revealed no indigo stones in their databases. Prein and Frondel specifically mention indigo stones as extremely rare.[3] 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?

MATERIALS AND METHODS

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. Although

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*Presented at the American Urologic Association Meeting, 2002.

he is known to have perpetrated such pranks in other medical literature using the *nom de plume* Egerton Y. Davis (Ex U.S. Army), the serious tone of his textbook cannot be minimized.[4,5] The science behind the study of urolithiasis is underscored by Marcet's famous quote . . . "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 (1817).[6] This historical investigation into the case of indigo calculus was done to illuminate the evidence and process leading to Dr. Osler's statement that indican has occasionally been found in calculi.[2]

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 databases, and read early urology textbooks in an effort to investigate Osler's claims of a blue urinary stone. *Index Medicus* was searched from 1920 backward to its inception in 1879 for the subject headings "calculous disease" and "indicanuria." There are two references to the use of indigo as a cathartic. Twelve textbooks of urology published prior to 1940 were reviewed for indigo calculi and indicanuria (Table 1). 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.

All of these data were correlated with Osler's historical record to gain insight into his thoughts on urolithiasis.[7] His publications, speeches, and addresses were reviewed, and biographies by Bliss[4] and Cushing[8] were read for further perceptions.

RESULTS

Osler's *The Principles and Practice of Medicine* was first published in 1892, when Osler was 41 years old while he was Professor of Medicine and the Physician-in-Chief at the Johns Hopkins University. The textbook's widespread popularity and durability through seven personalized editions attest to *Principles'* significance. Osler introduced a method of discussing diseases that has subsequently been adopted by many other medical authors. He began each section by defining the disease, introducing a brief historical note, followed by discussions of 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.[8] 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 cer-

Table 1. Urologic Textbooks Available for Review

Author(s)	*Title*	*Publisher*	*Year*
Eisendrath DN, Rolnick HC	Textbook of Urology for Students and Practitioners	JB Lippincott, Philadelphia	1928 (ed 4)
Greene RH, Brooks H	Diseases of the Genito-Urinary Organs and Kidney	WB Saunders, Philadelphia	1907
Keyes EL	Diseases of the Genitourinary Organs	D Appleton and Co, New York	1912
Lowsley DS, Kirwin TJ	Clinical Urology	Williams and Wilkins, Baltimore	1940
Casper L	A Textbook of Genito-Urinary Disease	P. Blakiston's Son and Co, Philadelphia	1906
Morton HH	Genitourinary Diseases and Syphilis	Physicians and Surgeons Book Co, New York	1924
Guiteras R	Urology, The Diseases of the Urinary Tract	D Appleton and Co	1912
Hertzler AE	Surgical Pathology of the Genito-Urinary Organs	JB Lippincott Co,	1931
Herman L	The Practice of Urology	WB Saunders	1938
Hinman F	The Principles and Practice of Urology	WB Saunders	1935
Young HH, Davis DM	Young's Practice of Urology	WB Saunders	1926
White HPW	Stone in the Urinary Tract	J & A Churchill, London	1929

tain solid constituents of the urine."[2] His sections on the etiology and pathology of stones 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.[2] It is this mention of a rare organic blue stone that drew our attention, as there is no modern recognition of this type of concretion.

Indigo is an organic blue pigment that has been 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. Far East trade in the dye derived from the *Indigofera* plant arose next. The monopolization of this blue dye trade led to 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 was rich in carbon compounds. His students, Kekulé and Bäyer, later synthesized several related benzene ring-containing compounds. Bäyer identified the chemical structure of indigo, synthesized it commercially, and won the Nobel Prize for chemistry in 1905.[13] The ability to produce indigo pigments from a cheap source such as coal tar undermined the international trade in indigo.[9]

Index Medicus has one published report on indigo bladder stones, from Egyptian mummy autopsies.[10] Pfister's paper was dated 24 years after Osler's textbook. The stones were analyzed chemically and were indigo blue. References in this manuscript include research work on indigo by Dr. Charles in Edinburgh and Dr. Virchow in Berlin. Osler had known ties to both men and has been noted in his biographies to have spent time at both of these centers. In addition, Pfister cites case report from America of a patient with an indigo calculus (more on this later).[11]

The indicanuria literature before Osler's textbook was lively.[12–15] Theories of the etiology of blue urine included a 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."[16] 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."[2]

The 12 urologic textbooks published 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 Eisenberg and Rolnick's *Textbook of Urology for Students and Practitioners,* (1928), they note that "indigo bladder stones are very rare." They likewise do not cite any references on these mysterious blue vesical concretions. The most significant reference in the textbooks comes from White's *Stone in the Urinary Tract* (1929). He states that "indigo is a substance which has given rise to one of the rarest kinds of kidney stones." He does not discuss the pathogenesis, associated conditions, or case findings. He does, however, reference a case report that was alluded to earlier in Pfister's paper by Dr. Forbes in Philadelphia.

On May 30, 1894, Dr. Forbes from the Jefferson Medical College presented a paper at the American Surgical Association in Washington, D.C.[17] The case involved the findings of a postmortem examination of a 27-year-old male suicide victim. During the autopsy, a mass was noted involving the patient's left kidney. In Dr. Forbes' words, "the left kidney surrounded by thick fibrous mass, involving the entire perinephric fat." A calculus was present involving the entire pelvis and one calix. The stone was a dark brownish-blue and, when drawn across white paper, it left a bright blue mark. 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, reported by Dr. Ord in 1879.[18] The article concluded by stating that this stone is preserved in the Jefferson Museum.[17]

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 Archivist. He is aware of this case report and has found the original steel engraving used to make the illustrations for Dr. Forbes's article (Figure 1; Thomas Jefferson University, MS19, box 4, ff6).

DISCUSSION

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. Three reports, two of which probably were known to Osler, can be identified. Osler's

FIG. 1. Original steel plate of illustration for Forbes article. Letters were used for size reference. (With permission of the Thomas Jefferson Medical College.)

extensive reading, cataloging of medical knowledge, and travels allowed him to become familiar with these rare medical cases. Urologic textbooks dating 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.[3] "Chronology, so the saying goes, is the last refuge of the feeble minded and the only resort for historians."[19]

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. The story of his first bout of renal colic is preserved in one of his resident's case reports.[1] His subsequent musings on stone passage were written during his later career while the Regius Professor of Medicine at Oxford (1905–1919). 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.[4] 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."[2] He might be predicting his own affliction in suffering from these recurrences, half a lifetime before the disease manifested itself.

That Osler's reference to indigo calculi was a prank, though possible, is unlikely. During Osler's first stone episode, Futcher 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.[1] 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*.[5] Osler expressed some degree of remorse for the printing of this trifle.[4] 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. It is known from the literature regarding indicanuria that certain infections are capable of causing blue voided urine, although now rarely encountered, and that ingested vital dyes can probably supersaturate the urine. There have been no solubility studies in the modern scientific literature showing that there is a point at which this threshold is crossed, resulting in urinary supersaturation, crystal deposition, and stone formation by this blue organic compound. 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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