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2.1 Bladder Pain Syndrome ... 30 Years Later

Enigmatic painful bladders and mysterious “ulcers” in the urinary bladder first appeared in medical publications in the early nineteenth century. Medical textbooks at the time drew a clear distinction between bladder neuralgia and bladder ulcers or lesions. However, by the beginning of the twentieth century, increasing use of the cystoscope may have led surgeons to focus on visible pathology, including ulcers and lesions, to the neglect of bladder neuralgia with invisible causes. Furthermore, Freudian theories prevalent at that period claiming women were “more prone to neurosis and hysteria” would have led to many women with urogenital pain being dismissed as psychosomatic and hysterical. While the original eighteenth to nineteenth century term “neurosis” referred to a neurological disorder, Freud’s version of neurosis inferred a psychological/hysterical disorder as used by Walsh in this book. This has regrettably been a cause of great harm to women and their health, particularly in urogenital fields, and has not entirely disappeared today.

In the nineteenth century, as noted by Walsh, “interstitial cystitis” was a term used to describe

a non-specific pathologic condition with inflammation in interstitial tissue caused by many diseases, disorders or trauma. The first mention of this term (found so far) was by Samuel D. Gross in 1876. In Germany, however, Maximilian Nitze was writing about a bladder disorder with frequency, pain and inflammatory ulceration of the mucosa which he described as “cystitis parenchymatosa”, a term which was not to survive, but which was, however, used by Howard Kelly in 1898 to describe “when inflammation extends into the muscular vesical wall”.

2.2 Howard Atwood Kelly (1858–1943): Pioneer in the Irritable Bladder

The Johns Hopkins Hospital in Baltimore, opened in 1889, was a centre of excellence in the United States. Howard Kelly, head of the new gynaecology and obstetrics department and Guy Hunner’s boss, had a special interest in female urology and this laid the foundation for Guy Hunner’s work with patients with a painful bladder. Howard Kelly, who had travelled extensively in Europe, took the Nitze cystoscope back to the Johns Hopkins Hospital in Baltimore and developed his own air distension version. Kelly had an interest in what he termed the irritable bladder: “A differential diagnosis must be made between cystitis and an irritable bladder or a hyperemia of the trigonum. In an ‘irritable

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bladder' there is no inflammation and there is no pus in the urine, and no inflammatory area is seen," he wrote in 1922. He further noted that "the condition is dependent as a rule upon abnormal sensibility of the nerves of the bladder either at their ending or at some point in their course. With this anatomical basis a number of conditions bring about the disturbance which would not cause it in a healthy adult". With regard to treatment, he recommended that "where the central nervous system is involved, the treatment should be directed towards this." This was remarkably forward thinking at the time, bearing in mind that it is only in recent years that researchers have been investigating the "new" concept of central sensitization. Like others, Kelly had already discovered that "such items of diet as tomatoes, fruits, or acids, should be avoided when the patient finds that they aggravate her condition".

2.3 **Guy Leroy Hunner (1868–1957): Bladder Ulcers and Lesions**

When Guy Hunner joined Howard Kelly's department, he consequently had every opportunity to study urological as well as gynaecological disorders in women. In 1899, Hunner was given leave by Kelly for a 4-month study visit to Europe to familiarize himself with the latest medical knowledge and insights. Endoscopy was now rapidly becoming all the rage in Europe, with the cystoscope opening up new horizons in urology. Eminent surgeons, including Hurry Fenwick in London, had published papers on perforating ulcers and simple solitary ulcers of unknown cause and this may have caught the interest of Guy Hunner. However, Hunner felt that most of the ulcers he was seeing differed from Fenwick's simple solitary ulcers. Guy Hunner was the first person to publish a detailed report about painful bladders and to describe what he saw through the cystoscope, case by case. Since by 1930 Hunner wrote that he now

had over 200 patients, he was considered the expert in this field in the United States. While he concentrated on ulcer and lesion pathology, Hunner did not forget patients with pain, urgency and frequency in whom the inside of the bladder appeared normal. His papers of 1915 and 1918 were seen as the "guideline" for many decades and consulted extensively. This is probably the reason why the term Hunner's ulcer was passed down from generation to generation. Hunner reported in 1918 that his colleague Dr. Cullen had suggested the name "elusive ulcer" due to the difficulty in locating the ulcer part of the lesion, but in his own opinion "it fails to describe adequately the widespread character of the chronic inflammatory involvement of the bladder walls."

Walsh is of the opinion that Hunner's use of the term "ulcer" led people to think that the disease might be focal. However, Hunner himself did not think it was focal but widespread, as we have seen above. Hunner also made a clear distinction in his publications between lesions and ulcers. Since his study of more than 200 of these patients took place over a period of at least 20 years, during which time cystoscopes would have been continually improving, it is debatable whether his belief that he was seeing true ulcers was entirely due to poor vision from the cystoscope. However, any meaningful comparison between Hunner's time and the situation today is always going to be problematic since he worked in an era when disease, infection and trauma were rife, antibiotics had not yet been invented, and women were very prudish and would probably have waited a very long time before plucking up the courage to consult a physician and may have concealed some of the more embarrassing details.

However, there is little doubt that his widely consulted publications did result in generations of urologists looking specifically for true ulcers and it could also be conjectured that the resultant focus on ulcers and lesions may have contributed to subsequent neglect of the non-lesion group—the *tic douloureux*—for many years.

2.4 John R. Hand

A new milestone was achieved in 1949 when John R. Hand from the Portland Clinic published a detailed, comprehensive study (223 patients: 204 women, 19 men) and literature review of what he now called “interstitial cystitis”, noting “I am inclined to agree with Folsom’s pithy comment that when Hunner ‘delivered this child into the urologic world he did not name it as well as he described it’.” Hand felt that “until a better name is found, “interstitial cystitis” is the most suitable since it is the only name with sufficient latitude to cover a diagnosis of the early as well as the late stages of the process.” A year later, Seaman writes that the “term “interstitial cystitis” seems to epitomize the pathological picture better than the 14 other names by which it has been designated and which seem only to confuse the issue.” We now therefore see that “interstitial cystitis” has moved away from being simply a pathology and has become the name of a painful bladder disease with “lesions”.

Hand presented a grading system for lesions, subdivided into three grades. There was, however, no mention of “ulcers” and no reference to non-lesion painful bladders. He noted that some of their patients had now been treated with anti-bacterial sulfonamides introduced in the 1930s and that the new pioneering antibiotic penicillin had been tried on three patients.

When performing cystoscopy, Hand recommended that the bladder should be distended, emptied and distended a second time in order to avoid overlooking the early lesions of interstitial cystitis. He noted that on distention small discrete submucosal hemorrhages and dotlike bleeding points could be observed.

While numerous theories had been put forward concerning etiology, Hand was inclined to believe that interstitial cystitis is caused by a neurogenic factor. The proliferation of nerve tissue mentioned by Hand also caught the attention of Walsh.

Hand drew attention to comorbidities in these patients, noting that “allergies were more

common among the patients with interstitial cystitis than among those from the general admission.” He also reported that Fister drew attention to the striking similarity of some features of interstitial cystitis and Lupus erythematosus.

Like others before him, Hand noted that there is a large element of individual variation in these patients.

2.5 Campbell’s Urology 1978: “An Irritable Bladder in an Irritable Patient”

Interstitial cystitis received a huge boost in awareness when Anthony Walsh was invited to write Chap. 19 on Interstitial Cystitis for the 1978 edition of Campbell’s Urology where he famously described “an irritable bladder in an irritable patient”. Here too he notes that “the synonym ‘Hunner’s Ulcer’ has led many less experienced physicians to expect to see an ulcer at cystoscopy, and when no ulcer could be found, they erroneously failed to diagnose many genuine cases.” True ulceration is rarely seen, noted Walsh. In recent years, lesion expert Magnus Fall has described the Hunner’s Ulcer as a “vulnus” or wound seen only upon distension.

The tiny, punctate red dots seen after distension are “an experience that we describe as glomerulation”. However, he emphasized that glomerulation is not absolutely pathognomonic, since it has been seen after distension in patients with dyskinesia.

Despite Walsh’s warnings, the term Hunner’s ulcer continued to be used and to mislead, while glomerulation was adopted as a hallmark of interstitial cystitis and incorporated into criteria.

Until this point, patients with no lesions were considered to have an early stage of the lesion disease. However, in 1978 Messing and Stamey pointed out that “we have no direct evidence that the classic disease will eventually develop in patients in the early group”.

This was further reinforced in 1987 when Fall et al., describing interstitial cystitis as a heterogeneous syndrome, reported that they had observed clear differences between lesion and non-lesion disease which they considered to be two separate conditions and which, they emphasized, should be studied separately in clinical studies. This advice was unfortunately also largely ignored with a mixed bag of patients still participating in clinical studies and drug trials, rendering all results very questionable for years to come.

2.6 Interstitial Cystitis Association and the NIDDK

A major impulse was the founding of the Interstitial Cystitis Association (ICA) in 1984 in the United States by Dr. Vicki Ratner, an IC patient and orthopaedic surgeon. The ICA's success in sparking the interest of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) led to more coordinated research, an attempt to define the disease and the creation of strict diagnostic criteria for research purposes in 1987 at a workshop and later published in 1988. However, it was soon clear that the criteria needed to be modified since there was a risk of 20–40% of patients diagnosed with IC now being excluded. The revised criteria were published in the 1990 first edition of this book but not in a journal, resulting in many physicians being unaware of them. The 1987 criteria therefore continued to be used extensively worldwide including for clinical diagnosis which had never been the intention.

The Interstitial Cystitis Data Base (ICDB) Study eligibility criteria which were less stringent did not stipulate mandatory cystoscopy for participating patients. Consequently, once again no distinction was made between patients with or without Hunner lesions in studies.

By 1999 it was clear, according to Hanno et al., that strict application of NIDDK criteria would have misdiagnosed some 60% of patients believed by clinicians to have some form of

interstitial cystitis, although by this time it was starting to become somewhat unclear exactly what was meant by interstitial cystitis.

As the new millennium dawned, it was becoming evident that consensus was lacking between different parts of the world, with the USA interpreting the term IC more freely—to the extent that it could by no means be called a rare disease in the US—while the rest of the world was still following the more restricted interpretation of the NIDDK criteria. Whereas the NIDDK had previously been seen as the IC Oracle of Delphi, research was now going global with greatly increasing interest in East Asia focusing around Japan where the Society of Interstitial Cystitis of Japan (SICJ) was set up, followed by an East Asian (Japan, South Korea, Taiwan) IC study group. An international conference—ICICJ—organised in Japan in 2003 revealed many of the cultural and scientific differences which were hindering further progress. Shortly afterwards, a European IC scientific meeting was held and ESSIC was set up.

2.7 Standards and Guidelines

In its 2002 Standardization of Lower Urinary Tract Function, the International Continence Society (ICS) Standardisation Committee reserved the name IC for a specific diagnosis based on typical cystoscopic and histological features (unfortunately without clearly specifying these features), while using “painful bladder syndrome (PBS)” for patients with symptoms but no identifiable infection or pathology. Since this was rather unclear to many people, the name simply became IC/PBS or PBS/IC while study or drug trial patients continued to be a mixture of both lesion and non-lesion.

Sparks were soon to fly when ESSIC published Diagnostic Criteria, Classification, and Nomenclature for Painful Bladder Syndrome/Interstitial Cystitis: An ESSIC Proposal, but soon decided to abolish the name IC altogether and henceforth use the name “bladder pain syndrome”, as they announced at an NIDDK

conference held in 2006. There was an uproar, including from the now extensive international IC patient movement which had not been consulted on any of the name changes. Nobody had taken into consideration any potential impact on the patients of a name change with respect to licensing issues and reimbursement, or eligibility for social security and disability allowances. The new name did not go down too well in East Asia either where they felt that it excluded patients who felt bladder pressure or discomfort but not what the patient interpreted as pain. This led to the revival of an old ICS term “hypersensitive bladder” in East Asia. Hypersensitive bladder symptoms consist of either pain or pressure or discomfort in the bladder usually with urinary frequency day and night and an urgent need to void. In the East Asian IC study group’s Hypersensitive Bladder (HSB) concept, HSB and non-lesion IC are hypersensitive bladder disorders while Hunner lesion IC is an immuno-inflammatory disease. This study group believes that patients should not be treated as a single entity simply because they have similar symptoms.

Within the space of a decade, a flurry of diagnostic and treatment guidelines and standardisation documents appeared, none precisely the same, and some so long and convoluted as to be unreadable by the everyday urologist, let alone primary care. These included the European Association of Urology’s Chronic Pelvic Pain Guideline, The American Urological Association IC/BPS Guideline, more recently the United Kingdom Joint RCOG/BSUG Guideline on Management of Bladder Pain Syndrome which included a focus on primary care, the ICS Standard for Terminology in Chronic Pelvic Pain Syndromes, Japanese and East Asian guidelines on IC and hypersensitive bladder and the Chronic Pelvic Pain Syndromes taxonomy by the International Association for the Study of Pain (IASP), as well as papers published by the French Nantes research group on pelvic visceral hypersensitivity.

Despite many articles since 1978 warning that glomerulation was not a reliable criterion, no further action was taken until the publication of a

review paper by Wennevik et al. on the role of glomerulations in bladder pain syndrome. This concluded that there is no convincing evidence in the reviewed literature that glomerulations should be included in the diagnosis or phenotyping of bladder pain syndrome/interstitial cystitis and that glomerulations do not correlate with symptoms and are found in patients without bladder pain syndrome/interstitial cystitis. However, the East Asian IC study group announced that it would be continuing to record which patients develop what they term “mucosal bleeding after distension” (MBAD), but point out in their 2015 guideline update that MBAD and glomerulations are not identical. MBAD is bleeding from the bladder mucosa during drainage, while glomerulations are pinpoint haemorrhagic lesions or petechiae.

2.8 NIDDK MAPP Research Network

In 2008, the NIDDK, uncomfortably aware that expensive research in the past had produced no benefits for the patients, now opted for a different, wider approach when it launched its Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) research network project, aimed at gaining a better understanding of both interstitial cystitis/ bladder pain syndrome (IC/BPS) and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), now embracing a systemic—or whole-body—approach, investigating potential relationships between these conditions and other chronic conditions that are sometimes seen in IC/BPS and CP/CPPS patients, such as irritable bowel syndrome, fibromyalgia, and chronic fatigue syndrome. However, in phase I the MAPP research also failed to draw a distinction in its studies between lesion and non-lesion. This was remedied in phase II. A prominent role is now being played by research into phenotyping with the aim of sorting out the patients, currently bundled together. One aim is ultimately to find the most appropriate treatment for each subtype.

2.9 Ketamine Cystitis

The development in recent years of bladder pain, urgency and frequency often combined with very severe lesions in street ketamine users has led to ongoing research worldwide into this phenomenon. This is being closely followed by the IC/BPS world in the hope that it may generate new insights into lesions and shed light on why some users develop ketamine cystitis while others do not.

2.10 Basis for Research Is Consensus

The basis for meaningful research must be international consensus on nomenclature, definitions and criteria, while allowing for flexibility for clinical purposes, with all stakeholders involved including patient organisations since they are an invaluable source of knowledge about the full spectrum of patients and the impact in practical terms. [TAU] This consensus must therefore be an important goal.

2.11 Awareness and Information

Thanks to the drive by both medical societies and patient organisations there is now more awareness of not only IC/BPS and its comorbidities, but also of the sexual, social and emotional impact of the disease on the patient. Many books have been published for both patients and the medical world while the advent of the Internet has opened up a vast store of electronic information that Walsh could never have envisaged.

However, with urology societies tending to focus increasingly on oncology and male problems, it is essential to get more information and guidance out to (uro)gynaecologists. Today, with all physicians faced with less time and more patients, guidelines must be succinct and freely accessible online for quick and easy reference and importantly include information for primary care. Urologists and urogynaecologists also need more information about comorbidities

so as to know when and to whom to refer their IC/BPS patients. A multidisciplinary approach is crucial for patients with IC/BPS and comorbidities.

2.12 Treatment: Right Treatment for Right Patient

Since Hunner's time, every imaginable treatment has been tried, many based on different theories. It has been estimated that over 180 treatments have been tried so far, a clear indication that something is very wrong. Everything works in a few patients, nothing is effective in all. Treatment is therefore highly individual.

Lesions are proving easier to treat than non-lesion bladders so these must be diagnosed at the earliest possible stage. To facilitate this, a comprehensive atlas of lesions would be of great value.

It is the large group of non-lesion IC/BPS patients which now urgently needs phenotyping so as to find the *right treatment for the right patient* at the earliest possible stage.

Above it, it should be remembered that a bladder disease like IC/BPS with pain, urgency and frequency can turn a normal person into an anxious, stressed, depressed recluse. Therefore, as Guy Hunner was fully aware, an important part of treatment for all patients is empathy and understanding.

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<http://www.springer.com/978-3-319-61448-9>

Bladder Pain Syndrome – An Evolution

Hanno, P.M.; Nordling, J.; Staskin, D.R.; Wein, A.J.;
Wyndaele, J.J. (Eds.)

2018, VII, 175 p. 177 illus., 108 illus. in color.,
Hardcover

ISBN: 978-3-319-61448-9