

## INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME HISTORICAL OVERVIEW

*“Previous to the latter half of the nineteenth century but little was known about diseases of the urinary apparatus in women. And while the relatively more urgent and dangerous diseases of the male organs had exacted the closest attention, the modesty of women, as well as the inaccessible nature of the affections, conspired to hinder an earlier scientific investigation of their genito-urinary organs.”*  
(Howard Kelly, *Operative Gynecology*, 1912)

In 1808, Philip Syng Physick, a renowned surgeon from Philadelphia, was reported as describing a painful inflammatory bladder disorder with an *“ulcer in the neck of the bladder”*, producing the same symptoms as stone (a common cause of bladder pain at that time). In 1836, the Philadelphian surgeon Joseph Parrish described the condition as *“tic douloureux”* of the bladder, a term commonly used for trigeminal neuralgia, which he attributed to his mentor Philip Syng Physick. He wrote: *“I have known instances of great suffering in the urinary organs, from this form of disease”*.

In the same year in France, Louis Mercier wrote about unusual and perplexing perforation of the bladder from *“ulcers”* in males for which he could find no cause, there being no stone, no venereal history and no sign of tuberculosis.

The earliest record of the term interstitial cystitis discovered so far can be found in *“A Practical Treatise on the Diseases, Injuries and Malformations of the Urinary Bladder, the Prostate Gland and the Urethra”* by Samuel D. Gross, Professor of Surgery in Philadelphia, 3<sup>rd</sup> Edition revised and edited by his son Samuel W. Gross and published in 1876. In the section Diseases of the Urinary Organs, Part I, Chapter I (Inflammation of the bladder and its results), he writes: *“When all the coats are implicated, it is termed interstitial, or parenchymatous cystitis...”*

Two years later, in 1878, the term interstitial cystitis appeared again in the first edition of a book on diseases of the female urethra and bladder in which Alexander J.C. Skene, a gynaecologist from Brooklyn, described a bladder condition characterized by inflammation. *“When the disease has destroyed the mucous membrane partly or wholly and extended to the muscular parietes, we have what is known as interstitial cystitis”*, wrote Skene.

This was echoed by Van Buren and Keyes in 1880 who explained:

*“Inflammation of the bladder, according to the anatomical portion of its walls involved, is known as:*

- *Cystitis mucosa – catarrh of the bladder*
- *Interstitial cystitis*
- *Peri-cystitis; epi-cystitis.*

*These varieties, however, do not demand detailed and separate descriptions, since they follow one upon the other as grades of intensity of the same morbid process.”*

In Germany, Maximilian Nitze (1848-1906), a founding father of modern urology, described the symptoms of a bladder disorder with frequency, pain and inflammatory ulceration of the mucosa, calling it *“cystitis parenchymatosa”* that caused *“heftige Beschwerden”* in the patients, published in a textbook in 1907 shortly after his untimely death at the age of only 57 years.

By 1912, the effect of diet was already attracting attention with the Boston gynaecologist Howard Kelly writing: *"Such articles of diet as tomatoes, fruits or acids, should be avoided when the patient finds that they aggravate her condition"*.

Meanwhile, the invention of the cystoscope in Europe was revolutionising bladder investigation, paving the way for Guy Hunner and his contemporaries to examine the bladder in greater detail than hitherto possible in living patients - rather than after their demise - without cutting the bladder open.

Guy Leroy Hunner, a Boston gynaecologist, described this "ulcerative", inflammatory bladder disease in great detail for the first time in a series of papers, the first being published in 1914 (republished in 1915). In this first paper, he writes:

*"While cystoscopy usually reveals only one inflammatory spot, there may be two or three granulation areas near together or somewhat separated, and operation usually reveals a more extensive area of inflammation than was appreciated by cystoscopy. The ulcer area may be easily overlooked and the attention may first be arrested by an area of dead white scar tissue. In the neighbourhood of this scar-looking area, one sees one or more areas of hyperemia which, on being touched with a dry cotton pledget, or with the end of the speculum, bleed and first show their character as ulcers. In other cases, or perhaps at subsequent examination on the same case, the ulcer may be well defined as a deeply red area with granulating base and with congested vessels surrounding the area. In none of the cases has an individual ulcer area been more than a half centimetre in diameter, although two or three such ulcers have at times been grouped in a larger inflammatory area."*

By 1918, not only was cystoscopic technology improving, but Hunner was gaining in experience and had many more patients. In his paper on the "Elusive Ulcer of the Bladder", he now gives more extensive descriptions of the cystoscopic picture: *"These ulcer areas are always small, usually measuring not more than 5mm. in diameter. They may be linear and measure from 0.5 to 2 cm. in length and from 1 to 2 mm. in width and may thus resemble the mouse-eaten linear ulcer not infrequently found in a tuberculous bladder. Two or three minute ulcers may be found in a group and they may be surrounded by a small red area of edema. The ulcers always appear to be superficial, and I have never seen them covered with necrotic membrane or urinary salts and have never seen them present a picture suggesting malignancy. The ulcer area may or may not be surrounded by a zone of radially converging vessels. One may find a minute ulcer with or without edema around it, and in another portion of the mucosa an edema area without an appreciable ulcer. These edema areas are generally seen immediately after the patient has been having an unusually bad period of bladder symptoms with much strangury."*

These "ulcers" came to be known as "Hunner's ulcers", although it was realized very early on that the term "ulcer" was a misnomer since it did not in fact concern a true ulcer but a vulnus and was frequently described by his contemporaries as a lesion. Hunner was using either the Nitze or Kelly cystoscope, but vision in those days was relatively poor and this may have been one of the reasons he thought he was seeing ulcers. However, his description of lesions remained the gold standard for many years.

Guy Hunner had deep empathy with his patients, describing their pain as follows: *"The pain is often of the most extreme grade, the patient complaining of a jabbing or stabbing knifelike pain or of a sensation of a jagged, sharp stick in the bladder."* One of his patients *"often had such extreme urgency that she had to leave a streetcar in order to enter the nearest house and ask for permission to void."*

Floyd Keene, gynaecologist of Philadelphia and a contemporary of Hunner, wrote a paper on “Circumscribed Pan-mural Ulcerative Cystitis” published in 1920 in which he described the bladder as having a “flea-bite” appearance in one or more areas.

In 1944 Cristol wrote about 78 cases of interstitial cystitis in men, and in 1950 Heslin also wrote on IC in male patients.

In 1946, on the other side of the world in New Zealand, Dr Patrick A. Treahy (1898-1963) published a remarkably detailed article on Interstitial Cystitis focusing on ulcers or lesions, noting that *“the chief complaints are intense urgency, pain and frequency”*. And while the condition may be suspected from the history, *“cystoscopy is necessary for confirmation.”*

While there were many more publications on this disorder on both sides of the Atlantic in English, French and German at this period, it was John R. Hand who published the first really comprehensive paper on the subject with a report on 223 cases (204 women and 19 men) in 1949. Hand divided the interstitial cystitis patients into 3 grades, based on the severity of the cystoscopic findings: Grade I represents minimal bladder involvement, Grade II represents a more advanced stage of the disease, Grade III represents the most advanced stage of the disease. Hand also described submucosal hemorrhages: *“On distention there were small discrete, submucosal hemorrhages, showing variations in form. Near the trigone, for example, there were dot-like bleeding points”* (the term “glomerulations” was only coined much later in 1978 by Walsh). The symptoms were described as pain, frequency day and night and extreme urgency. At this period, it was still assumed that milder cases would eventually progress to lesions.

Although earlier writers – including Guy Hunner - were aware of a possible association with rheumatic diseases, Hand emphasized that *“allergies were more common among the patients with IC than among those from the general admission.”*

Like all of his colleagues, Hand was also concerned with the name of the disease and wrote: *“For some time I have also been impressed with the inadequacy of the many names which have been given to this disease. And after considerable thought, 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”*. He continues: *“Without doubt, some phase of the disease gives justification for each of its many names. But no one name yet proposed is wholly satisfactory because it fails to take into account the changing picture of the disease. However, until a better name is found, ‘interstitial cystitis’ is the most suitable...”* Hand can be said to have brought IC into the modern era.

In 1951, the term “painful bladder” first appeared, introduced by J.P. Bourque from Canada as an umbrella term for all disorders causing pain in the bladder including IC.

Two articles on IC in children by Harold McDonald appeared in 1953 and 1958, followed by an article in 1960 on the same topic by Chenoweth.

In 1970, in a paper on new clinical and immunological observations, Oravisto and colleagues wrote: *“Although interstitial cystitis is fairly uncommon, it is not rare and, in our experience, mild and atypical cases readily escape detection”*. Oravisto noted the high frequency of drug hypersensitivity in these patients.

In 1978, a milestone was reached when Chapter 19 of Campbell’s Urology was entirely devoted to interstitial cystitis. Author Anthony Walsh described IC as a *“disease of extremes: extremely severe symptoms; extremes of underdiagnosis; etiologic theories varying from the abstruse to the*

*fashionable; treatment ranging from the alpha of vitamin prescription to the omega of radical bladder substitution surgery; and sadly often, extreme confusion in medical thinking,”* much of which is still valid today. Walsh felt that the term Hunner’s ulcer should be abandoned because *“it is seriously misleading”* and notes that *“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”*.

Walsh appears to be the first to describe punctate red dots as “glomerulations” but questions the specificity of glomerulations since *“glomerulation is not absolutely pathognomonic since it has been seen after overdistension in patients with dyskenesia”*. However, despite Walsh’s possible doubts, glomerulations mistakenly continued to be considered a hallmark of IC until the mid-1990s when their diagnostic value came into question once again.

Walsh famously described IC as *“an irritable bladder in an irritable patient”*.

Also in 1978, Messing and Stamey reported in great detail on a retrospective review of 52 patients with IC and felt that the majority of patients do not have Hunner’s ulcer. Like Walsh, they stated that *“we believe that the synonymity of Hunner’s ulcer with interstitial cystitis has done more to prevent recognition of this disease than any other single factor”*.

It is indeed most probably this historic association between Guy Hunner's ulcers and IC that has resulted in many patients with the non-ulcerative type remaining undiagnosed and untreated over so many decades.

In 1987, in a landmark paper, Magnus Fall and colleagues described interstitial cystitis as a *“heterogeneous syndrome”*. They also reported observing marked clinical differences between ulcerative (classic) and nonulcerative interstitial cystitis: *“These 2 conditions appear to represent separate entities and should be evaluated separately in clinical studies”*. Unfortunately, this went unheeded and all patients with or without lesions continued to be bundled together.

Also in 1987, encouraged by the Interstitial Cystitis Association (ICA) founded in the United States of America in 1984, the NIDDK in the USA drew up a first consensus definition of IC, revised in 1988. These criteria were specifically intended for research purposes to provide a common basis for much-needed studies and allow comparison between the studies. While the criteria were never intended as a definition for the clinician, due to the lack of any other guidelines for clinical diagnosis, they were widely used for the diagnosis of patients in a clinical setting. It was later estimated that some 60% of patients with IC symptoms failed to meet these strict criteria, resulting in many patients remaining undiagnosed and consequently untreated. The irony of the situation is that while doctors in the United States mainly stopped using the NIDDK criteria for clinical diagnosis, doctors in other parts of the world continued to adhere to them rigidly due to the lack of any other clear guidelines.

An interesting aspect of the NIDDK criteria was that pain was not compulsory: it required either pain or urgency. However, this was likely because urgency in a hypersensitive bladder at that time was termed “sensory urgency”.

Although the name painful bladder (disease) had been around since the early fifties, it was only introduced into standard terminology in 2002 by the International Continence Society (ICS), defining it as *“the complaint of suprapubic pain related to bladder filling, accompanied by other symptoms such as increased daytime and night-time frequency, in the absence of proven urinary infection or other obvious pathology”*. They reserved the term interstitial cystitis for patients with *“typical cystoscopic and histological features”*. However, the ICS unfortunately did not specify exactly what these typical features were. This led to usage of the combined term IC/PBS or PBS/IC, due to the fact that doctors found it difficult to understand what the distinction was supposed to be between IC and PBS,

particularly in countries where it was not customary to perform cystoscopy and/or biopsy in all patients. This definition of PBS was shown by J. Warren to have only 64% sensitivity.

The same ICS paper redefined the term “urgency” – previously subdivided into motor urgency (sudden urgency) and sensory urgency in a hypersensitive bladder – now making all urgency “sudden” and “for fear of leakage”, so the term could only be used for overactive bladder syndrome. Urgency was then cut out of all IC definitions and consequently out of research.

In 2006, the European Society for the Study of IC/PBS (ESSIC) designed a type-classification system according to findings at cystoscopy and biopsy and caused some controversy on announcing that it preferred to use the name bladder pain syndrome (BPS) which was a new name taken from the urogenital pain taxonomy (classification) of the International Association for the Study of Pain (IASP), a taxonomy also used in EAU Guidelines for chronic pelvic pain.

ESSIC’s definition in 2008 was as follows: *BPS would be diagnosed on the basis of chronic (>6 months) pelvic pain, pressure or discomfort perceived to be related to the urinary bladder accompanied by at least one other urinary symptom like persistent urge to void or frequency. Confusable diseases as the cause of the symptoms must be excluded. Further documentation and classification of BPS might be performed according to findings at cystoscopy with hydrodistension and morphological findings in bladder biopsies. The presence of other organ symptoms as well as cognitive, behavioural, emotional and sexual symptoms should be addressed.*

A problem in the ESSIC and other definitions at that time (and still today) was “Persistent urge”, a term newly coined in the USA to replace the now banned sensory or painful urgency. But ... persistent urge to void does not mean an urgent need to find a toilet.

In 2008, the NIDDK launched an initial 5-year multi-centre research programme, followed by a second research programme, entitled the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) with an innovative shift in research focus. This research project was to study both interstitial cystitis (IC) and chronic prostatitis (CP/CPPS) in a wider systemic framework, exploring in more detail the relationships and overlap with disorders that often co-exist such as fibromyalgia, irritable bowel syndrome, chronic fatigue and vulvodynia and asking whether these associated disorders can provide additional insights into IC/BPS or CP/CPPS. The primary objectives of the MAPP included: to understand the underlying disease pathophysiology and risk factors through targeted epidemiological studies and use of biological samples; and to provide a translational foundation for the development of therapies.

An important part of these studies was to be the *phenotyping* (clinical characterization into types) of patients participating in the studies. The ultimate aim is to arrive at optimum treatment for the individual patient and avoid the current “hit-or-miss” approach. In connection with this study, a new term was introduced by the NIDDK: the Urologic Chronic Pelvic Pain Syndromes (UCPPS). For more information on the MAPP study, visit: <https://www.mappnetwork.org/>

The NIDDK MAPP IC Inclusion Criteria are as follows:

- *Females or males having an unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of at least 3 consecutive months’ duration, in the absence of infection or other identifiable causes.*
- *Scoring at least 1 on the frequency scale and at least 1 on the pain, pressure, discomfort scale.*

The “snowflake hypothesis” appeared in 2009 in relation to both IC and CP, based on the concept that no two patients are the same, just like snowflakes which are all different but still snowflakes. This led to a pilot clinical phenotyping system developed by Nickel, Shoskes and Irvine-Bird known as **UPOINT**. The purpose of this pilot phenotyping system was to classify patients with IC according to clinically relevant domains or subtypes (phenotypes) with the ultimate aim of optimizing therapy and improving outcomes. These UPOINT domains were: **U**rinary, **P**sychosocial, **O**rgan Specific, **I**nfection,

Neurologic/Systemic, Tenderness. However, in 2018 this was changed for IC/BPS to **INPUT**: Infection, Neurologic/systemic, Psychosocial, Ulcers and Tenderness of muscles.

The Society of Interstitial Cystitis of Japan (SICJ) and a group of East Asian countries (Japan, Korea, Taiwan) both published detailed guidelines in 2009, in which they both proposed a new symptom complex to be known as Hypersensitive Bladder Syndrome (HBS). This would be a clinical entity that is more inclusive than pain syndromes alone since it incorporates patients with and without pain. The HBS concept was slightly adjusted in 2013. They defined interstitial cystitis (IC) as a disease of the urinary bladder diagnosed by three conditions: 1) lower urinary tract symptoms, such as bladder hypersensitivity, urinary frequency, bladder discomfort and bladder pain; 2) bladder pathology such as Hunner's ulcer and mucosal bleeding after over-distension; and 3) exclusion of confusable diseases such as infection, malignancy and calculi of the urinary tract. They created the umbrella term of "frequency/urgency syndrome" characterized by frequency (frequent voiding) and urgency (strong desire to void). This is an inclusive term incorporating overactive bladder syndrome, hypersensitive bladder and other conditions associated with frequency and urgency.

In 2011, the American Urological Society (AUA) decided to adopt the name IC/BPS in its guideline *"Diagnosis and Treatment of Interstitial Cystitis/Bladder Pain Syndrome"*. In the field of diagnosis, it placed the emphasis on exclusion of other diseases or disorders and the symptoms of the patient. The definition it adopted is as follows: *"An unpleasant sensation, (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than six weeks duration, in the absence of infection or other identifiable causes."* In this AUA guideline, the terms IC and BPS are used synonymously.

This guideline is regularly updated and can be accessed at:

[https://www.auanet.org/guidelines/guidelines/interstitial-cystitis-\(ic/bps\)-guideline](https://www.auanet.org/guidelines/guidelines/interstitial-cystitis-(ic/bps)-guideline)

In its 2012 updated Guidelines on Chronic Pelvic Pain, the European Association of Urology (EAU) used the term bladder pain syndrome with the following definition: *"bladder pain syndrome should be diagnosed on the basis of pain, pressure or discomfort associated with the urinary bladder, accompanied by at least one other symptom, such as daytime and/or night-time increased urinary frequency, the exclusion of confusable diseases as the cause of symptoms, and if indicated, cystoscopy with hydrodistension and biopsy."* The term IC is reserved for Hunner's lesion as a specific type of chronic inflammation of the bladder.

At the 1<sup>st</sup> Sensory Bladder Meeting held at Les Pensières, Fondation Merieux, Veyrier du Lac, France, 22-23 June 2012, J-J Labat from Nantes presented the French hypersensitivity proposal:

- *Non-painful visceral hyperactivity syndrome due to visceral hypersensitivity (bladder, bowel)*
- *Painful pelvic visceral hypersensitivity (bladder, bowel, vulva, urethra, prostate)*
- *Pelvic non-visceral hypersensitivity (musculoligamentous trigger points, bone (bone tenderness), skin, mucosa (hyperpathia, superficial allodynia)*

The book "Bladder Pain Syndrome, A Guide for Clinicians" by the ESSIC group was published in 2013.

The Joint meeting of the 3<sup>rd</sup> International Consultation on Interstitial Cystitis (ICICJ3) and the ESSIC Annual Meeting 2013, held in Kyoto Japan 21-23 March, 2013, recommended splitting off Hunner lesion and calling it by its historic name interstitial cystitis, reserving the term bladder pain syndrome for non/lesion patients. However, the East Asian countries did not like use of the pain term since they believe that patients do not necessarily interpret discomfort, pressure and unpleasant sensations as being pain and for this reason they use the term hypersensitive bladder. The meeting emphasised that glomerulations should not be considered diagnostic, they are not specific to IC/BPS and at present no-one knows what causes them or what their significance is. It was also stressed

In 2015, Wennevik and colleagues concluded that there are no convincing data to show that the presence of glomerulations is specifically related to BPS/IC in Wennevik GE, Meijlink JM, Hanno P, Nordling J. The role of glomerulations in Bladder Pain Syndrome – A review. *J Urol* 2016 Jan 01;195(1):19-25

In 2018, the book Bladder Pain Syndrome – an Evolution. Edited by P.M. Hanno, J. Nordling, D.R. Staskin, A.J. Wein, J.J. Wyndaele was published.

Meetings of ICICJ/SICJ in Kyoto and ESSIC in Florence in 2018 concluded that the lack of international consensus on the name and definition is indeed a problem because consistency in use of terminology is a basic requirement for clear communication in any field of medicine and is essential for international research. But first we need to understand exactly what disease (or diseases) it is that we are trying to communicate! Further phenotyping or subtyping should help to point the way to better treatment. In the meantime, for the sake of continuity and clarity for patients and for others seeking information, the patient organizations are mainly continuing to use the traditional name interstitial cystitis (IC), sometimes in combination with bladder pain syndrome (IC/BPS) or painful bladder syndrome (IC/PBS) and in East Asian countries hypersensitive bladder (HSB).

In 2019, several papers were published from different parts of the world recommending that Hunner Lesion Disease should be considered a separate entity from non-lesion IC/BPS. This continued into 2020 with a paper published by an ESSIC working group noting that “It is time to accept that classic IC with Hunner lesions and BPS always should be evaluated separately in science as well as in clinical routine.”

Also published in 2020 was a paper calling for the reinstatement of sensory urgency so as to help ensure that researchers and drug developers are actually researching the real disease suffered by real patients. Meijlink J. An urgent case for sensory urgency: A patient perspective. *Neurourol Urodyn*. 2020 Sep;39(7):2008-2010. doi: 10.1002/nau.24457. Epub 2020 Jul 10. PMID: 32648972.

Hanno *et al* published a comment in 2020 urging that “*It is time to move on with a new paradigm. The benefits to our patients’ now and future progress in drug development and knowledge beg for a separation of HLD from BPS. To do otherwise is to continue a prolonged disservice to patients.*”

To add to the global terminology confusion, the IASP ICD-11 task force for chronic pain recently introduced the term chronic primary visceral pain to include chronic primary bladder pain syndrome.

This classification system introduces chronic pain as a disease in itself for the first time (<https://icd.who.int/en>). This is echoed by the EAU’s revised chronic pelvic pain guideline which now refers to primary bladder pain syndrome (<https://uroweb.org/guideline/chronic-pelvic-pain/>).

The intention of ICD is that primary should be used when there is no identifiable cause of the disorder. However, Hunner lesion does not appear to have been explicitly excluded and that is indeed identifiable.

A question is therefore: should it in fact be “primary” or should it come under “chronic secondary visceral pain”, or should it be split up between the two?

However, ICD-11 still has “interstitial cystitis” under Genitourinary Diseases:

GC00.3 Interstitial cystitis

*A condition characterised by inflammation of the urinary bladder and ureters. This condition may be associated with a malformation of, or injury to, the bladder epithelium, infection with toxins, an autoimmune reaction, or an allergy. This condition may also present with Hunner ulcers diffuse*

*glomerulations affecting all quadrants of the bladder mucosa, mild to severe chronic bladder pressure, bladder pain, urgency to urinate, and low volumes of urine.*

While the description here is not entirely up-to-date, it is at least understandable for clinicians around the world.

In 2023, ICS and ICUD published the 7<sup>th</sup> Edition of the book Incontinence, with Chapter 18 providing a comprehensive history and update on diagnosis and treatment of Interstitial Cystitis/Bladder Pain Syndrome, compiled by an international committee chaired by Philip Hanno, MD.

*See also for history:*

Meijlink JM. Interstitial cystitis and the painful bladder: a brief history of nomenclature, definitions and criteria. Int J Urol. 2014 Apr;21 Suppl 1:4-12. doi: 10.1111/iju.12307. Review.

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