

Comment

Towards a new paradigm in bladder pain syndrome and interstitial cystitis

Philip Hanno¹ , Magnus Fall², Jane Meijlink³ and Jørgen Nordling⁴

¹Department of Urology, Stanford University School of Medicine, Stanford, CA, USA, ²Department of Urology, Institute of Clinical Sciences, Sahlgrenska Academy at the University of Gothenburg, Göteborg, Sweden, ³International Painful Bladder Foundation, Naarden, the Netherlands, and ⁴Department of Urology, Herlev and Gentofte Hospital, University of Copenhagen, Herlev, Denmark

Hunner lesion disease (HLD), termed ‘interstitial cystitis’ (IC) since the description of Guy Hunner’s ‘elusive ulcer’ a century ago, referred to a specific disease with specific findings on endoscopy associated with a typical symptom complex. Unfortunately, there were many patients with a similar symptom presentation who did not meet this restricted definition. Some would have infection, some would have overactive bladder, some would suffer from the effects of pelvic radiation, and many would have no known aetiology or findings on evaluation other than the symptoms alone. Almost by a quirk of fate the latter group was thrown into the IC category in the second half of the century [1]. This has limited progress in terms of helping both cohorts of patients and left many patients with HLD undiagnosed and poorly treated. It is now time to admit what we do not know and not categorise all patients with similar symptoms under the rubric of IC.

The disunity in the urological community needs to be resolved without further delay. The diagnostic criteria of bladder pain syndrome (BPS)/IC are confusing. In hindsight, we have to acknowledge that these criteria unfortunately became even more bewildering after the important and ambitious 1987 National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) meeting [2], which sanctioned the prevailing view, *put forward without any evidence* that IC is one disease rather than potentially several disorders presenting with similar symptoms. IC could refer to almost anything related to bladder dysfunction and was in the eye of the beholder, or as Tage Hald commented ‘a hole in the air’. No longer was IC the well-defined disease described by Hunner early in the 20th century. This perception, to paraphrase Einstein, of a ‘unified theory of IC’ has prevailed and dominated much of the discussion. For decades identifying HLD was not considered to be particularly important. The diagnosis of IC did not require cystoscopy and treatment algorithms did not hinge on the finding of a HL. It is only during the last decade or so that the issue has been specifically highlighted, inspired by the work of the European Society for the Study of Interstitial Cystitis (ESSIC) [3]. This lack of interest is difficult to understand knowing the real long-term experience of the advantages of various

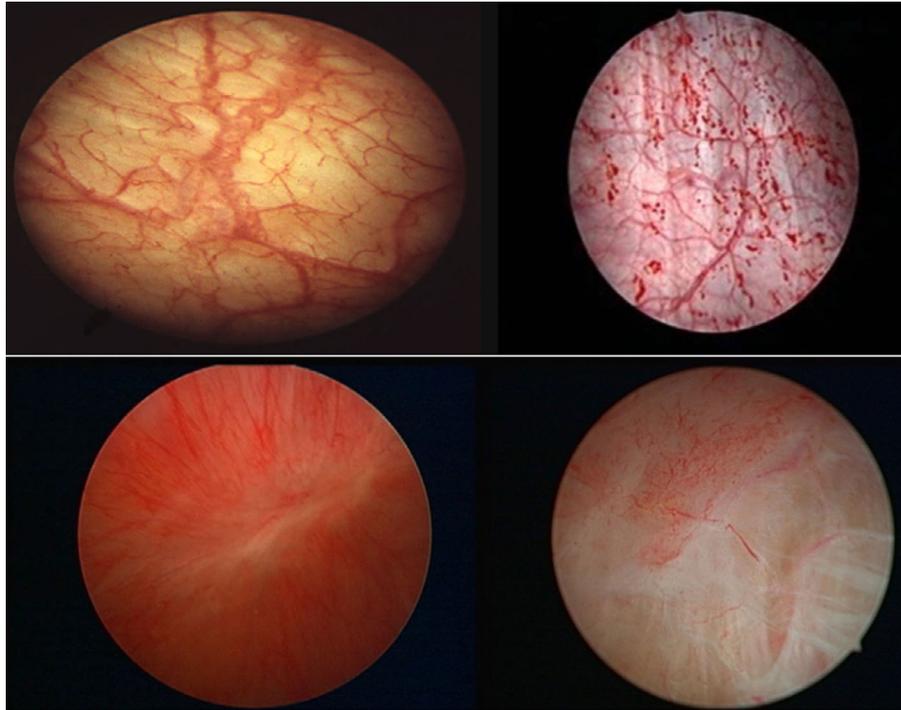
ablative techniques for HLD used since the 1970s [4]. Such techniques include transurethral resection (TUR), coagulation, and laser treatment and intravesical injections of steroids. For the sufferers of HLD identification of the lesion is crucial for diagnosis and improvement of quality of life (Fig. 1).

Once the HL is identified, now often by office cystoscopy, outcomes with the different types of local management are similar [5] and which technique to use is mainly up to the surgeon. Coagulation is easier to perform in the often thin-walled IC bladders and thus less risky than resection of lesions, although TUR has been proved to be safe in the hands of experienced resectionists. The advantage of having abundant tissue for the pathologist to examine and the completeness of ablation are possible advantages of TUR vs fulguration, at least in the research setting; the issue is fertile ground for future study.

Histopathology has been a parallel problem, but now there is renewed enthusiasm for subdividing painful bladder conditions [6]. Past clinical indifference to histopathological findings is remarkable given the multiple examples of dramatic histopathological differences between HLD and non-HLDs in numerous research publications. Such findings and differences may suggest disease mechanisms. Examples include (i) granulation tissue in the lamina propria and fibrosis involving the detrusor muscle in HLD specimens but not in non-HLDs; (ii) marked mast cell count increase together with a quite unique finding of mast cell migratory capacity in HLD, not existing in non-HLDs; (iii) lymphocyte activation patterns in HLD not found in non-HLDs; and (iv) additional cell elements such as plasma cells and macrophages, with inflammatory infiltrates located in proximity to intramural nerve fibres in HLD. How much more data do we need to merit the acknowledgement of fundamental differences in the patient with HLD from a patient with a non-HLD BPS? Who can deny the importance of separating these entities? And, finally, where are the data to support a continuum of a non-HLD developing into HLD? The data do not exist.

It is time to move on with a new paradigm. The benefits to our patients now and future progress in drug development

Fig. 1 Various cystoscopic features can be found in patients with BPS. Cystoscopy clockwise from left: normal bladder mucosa, glomerulations following bladder distension, HL before distension and after distension. To believe this is one disease in the absence of confirmatory data strains credulity.



and knowledge beg for a separation of HLD from BPS. To do otherwise is to continue a prolonged disservice to patients. The recent United States Food and Drug Administration (FDA) draft guidance (<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/interstitial-cystitisbladder-pain-syndrome-icbbs-establishing-effectiveness-drugs-treatment-guidance>) is one example that demonstrates that indifference prevails. We suggest that it is time for the urological associations of the world to add this concept to their guidelines, and time for government entities to give HLD its own diagnosis. Insight into an obvious fact is very late and many patients with HLD have gone undiagnosed for years.

Conflict of Interest

Dr Hanno reports working with Seikagaku on developing a new treatment for IC as a consultant for 3 years. No other authors have conflicts of interest to declare.

References

- 1 Messing EM, Stamey TA. Interstitial cystitis: early diagnosis, pathology, and treatment. *Urology* 1978; 12: 381–92
- 2 Gillenwater JY, Wein AJ. Summary of the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases workshop on interstitial cystitis,

National Institutes of Health, Bethesda, Maryland, August 28–29, 1987. *J Urol* 1988; 140: 203–6

- 3 van de Merwe JP, Nordling J, Bouchelouche P et al. Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis: an ESSIC proposal. *Eur Urol* 2008; 53: 60–7
- 4 Fall M, Nordling J, Cervigni M et al. Hunner lesion disease differs in diagnosis, treatment and outcome from bladder pain syndrome: an ESSIC working group report. *Scand. J Urol* 2020; 54: 91–8
- 5 Ko KJ, Cho WJ, Lee YS et al. Comparison of the efficacy between transurethral coagulation and transurethral resection of Hunner lesion in interstitial cystitis/bladder pain syndrome patients: a prospective randomized controlled trial. *Eur Urol* 2020; 77: 644–51
- 6 Akiyama Y, Luo Y, Hanno PM et al. Interstitial cystitis/bladder pain syndrome: the evolving landscape, animal models and future perspectives. *Int J Urol* 2020; 27: 491–503

Correspondence: Philip Hanno, Department of Urology, Stanford University School of Medicine, 300 Pasteur Drive, Suite S-287, Grant Building, 2nd Floor, Stanford, CA 94305-5118, USA.

e-mail: pmhanno@stanford.edu

Abbreviations: BPS, bladder pain syndrome; HL(D), Hunner lesion (disease); IC, interstitial cystitis; TUR, transurethral resection.