

## Peer Review File

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### Review Comments

#### Reviewer A:

##### Minor Revision

Dear authors congratulations for your article. I think that it should be classified as a narrative review of the literature. As for the video it is nicely explained however the pointer should be avoided to show the line that is read during the narration and at some points the sound is cut.

Reply: Thank you. The yellow pointer has been applied in all the videos. We receive no unfavorable comment in this matter for the videos of other manuscripts for this special series. We will re-examine the videos and see what we can do.

#### Reviewer B:

Thank you for having imagined the theory you described in this article. Three comments:

- Even if the IC/BPS definition by ICS seems very clear we all know that all these patients described not exactly the same symptoms. Sometimes it is not easy to distinguish a real painful pollakiuria (which could be an IC/BPS) from a chronic pelvic pain who has also pollakiuria.

Reply: Thank you. According to the ICS definition, “a chronic pelvic pain who has also pollakiuria” is in fact a “non-Hunner’s IC/BPS!.

- Hunner described what he called an ulcer in 1918 using a cystoscope with no cold-light equipment but only a light placed behind him. I am not sure that what we can describe with our modern equipment are the same lesions.

Reply: Thank you, but what you say is not a reason for rejecting this paper.

Moreover the recent literature suggests that bladder ulceration should no more be part of IC/BPS because it can be cured by a complete TURB or fulguration.

Reply: Thank you, but again, what you say is not a reason for rejecting this paper. Furthermore, TURP or fulguration cure have no part in the ESSIC or ICS definition.

Current thinking by ESSIC is that Hunner's IC/BPS is defined by symptoms of pain and one bladder dysfunction PLUS histological findings of mast cells, which both of our clinical studies conformed to.

- Your theory is based upon the results of two articles: one case report which need to be confirmed by a larger serie and a large serie which contain heterogenous patients according to the symptomatology which is described. In conclusion your theory is interesting but it needs to be confirmed by a robust multicentric study with clear inclusion criteria before being adopted.

Reply: Thank you. "a larger serie ", "heterogenous patients" The reviewer has delineated two research projects to test the theory further. We agree what we propose requires further testing as recommended by the reviewer. However, these comments have nothing to do with the present status of a theory.

The American Museum of Natural Science sets out the following criteria for a theory. We comment on each (in red type).

- "A theory is a well-substantiated explanation of an aspect of the natural world that can incorporate laws, hypotheses and facts."

COMMENT Karl Popper's dictum, was that one validated case (Scheffler's cure of a histologically validated case of Hunner's Ulcer IC/BPS) invalidates previous thought that such conditions were not curable. The 2<sup>nd</sup> paper by Goeschen comprised 198 women and there were clear inclusion criteria, those set out by the ICS and ESSIC for IC/BPS..

- A theory not only explains known facts; it also allows scientists to make predictions of what they should observe if a theory is true.
- Scientific theories are testable.

COMMENT Goeschen et al selected 198 women who presented with chronic pelvic pain from a previous data base who were treated by a posterior sling which repaired the uterosacral ligaments. These 198 women had 313 bladder symptoms, which fitted the ICS and ESSIC definitions of IC/BPS

- New evidence should be compatible with a theory.

COMMENT We tested data from another source, from Liedl et al., 616 women treated by uterosacral ligament repair. The cure/improvements reported were consistent with the ESSIC and ICS definitions. Again, chronic pelvic pain was associated with multiple symptoms of bladder dysfunction, again conforming to ESSIC and ICS definitions.

Liedl B, Inoue H, Sekiguchi Y, et al. Is overactive bladder in the female surgically curable by ligament repair? Citation: Cent European J Urol. 2017; 70: 51-57.

**COMMENT** It was tested again by surgical data from Petros. Again, the cure/improvements reported were consistent with the ESSIC and ICS definitions.

Petros PE, Richardson PA. Interstitial cystitis symptoms as defined are indistinguishable from posterior fornix syndrome symptoms cured by uterosacral ligament repair. Pelviperineology. 2021;40(3):145-153. doi:10.34057/PPj.2021.40.02.2021-7-5.

- If it isn't, the theory is refined or rejected. The longer the central elements of a theory hold—the more observations it predicts, the more tests it passes, the more facts it explains—the stronger the theory.

**COMMENT** So far, there has been no invalidation of our theory that IC/BPS may be one and the same as the posterior fornix syndrome.