Since the 19th century, searches for the pathogenesis of interstitial cystitis/bladder pain syndrome (IC/BPS) have concentrated on the bladder. However, recent work has shown that patients with IC/BPS are more likely than controls to have syndromes with symptoms beyond the bladder and even the pelvis. These findings suggest that research into IC/BPS etiology should not focus only on the bladder.

The sequence of investigation of nonbladder syndromes (NBSs) and IC/BPS has been similar to that for most medical research: case series generating hypotheses that are then tested in controlled studies. For instance, a often-cited survey of patients with IC/BPS showed an apparently high prevalence of fibromyalgia (FM), chronic fatigue syndrome (CFS), irritable bowel syndrome (IBS), allergy, asthma, vulvodynia, and several other diseases and syndromes.1 Recent controlled studies have confirmed most of these findings. We believe that these studies have integrated important facts into the knowledge of IC/BPS. The present report presents these facts, formulates the hypotheses they generate, and suggests pathways to test these hypotheses.

**THE FACTS**

Many NBSs are Associated With IC/BPS

Clauw et al2 were among the first to show that patients with IC/BPS were more likely than controls to have an NBS (ie, FM). Moreover, during the past 5 years, investigators compared patients with IC/BPS with controls for multiple NBSs. Wu et al3 identified 749 patients with IC/BPS diagnosed using the International Classification of Diseases (ICD). They compared them with 1498 randomly selected and matched controls.Significantly more IC/BPS patients had FM, IBS, chronic pelvic pain (CPP), endometriosis, depression, anxiety, and vulvodynia.

Clemens et al4 identified 239 women with ICD-coded IC/BPS and compared them with 717 matched controls. The incidence of myalgias, gastrointestinal symptoms, gynecologic pain, headache, back disorders, depression, and anxiety was significantly greater in IC/BPS patients than in controls.

In a study of the risk factors for IC/BPS discussed later in the present report, Warren et al5 demonstrated that significantly more patients with IC/BPS than matched controls had these 11 antecedent syndromes: FM, CFS, IBS, sicca syndrome, CPP, migraine, allergies, asthma, depression, panic disorder, and vulvodynia.

In several urology practices on 3 continents, Nickel et al6 found a significantly greater prevalence of self-reported FM, CFS, IBS, migraine and tension headaches, vulvodynia, temporomandibular disorder, and low back pain in 207 women with IC/BPS than in 117 controls, as well as significantly more IC/BPS cases with depression and anxiety.7

A recent review confirmed that FM, CFS, and IBS are associated with IC/BPS.8

Baranowski et al9 suggested a 3-group framework to assess IC/BPS and NBSs. One group would have only bladder symptoms. The second would have symptoms perceived in other pelvic organs, thus possibly representing central sensitization (ie, pain generated from 1 pelvic organ that is perceived in other pelvic sites because the second order neurons in the spinal cord also receive signals from those sites).10 The third group would be patients with IC/BPS with systemic syndromes, a group requiring a mechanism beyond the lower spinal cord to explain these anatomically remote symptoms.

Two cited studies distributed IC/BPS cases using the 3-group framework. Warren et al10 noted that 7% of patients had only IC/BPS (ie, with none of the associated syndromes). Only 2% had pelvic syndromes (ie, CPP, IBS, vulvodynia), but no systemic syndromes. The remainder, 91%, were in the third, systemic, category with...
syndromes such as FM, CFS, or migraine.\textsuperscript{5} Nickel et al\textsuperscript{6} used 3 NBSs to assign patients with IC/BPS to phenotypes that roughly corresponded to the groups denoted by Baranowski et al\textsuperscript{2}: IC/BPS only, regional pain (IC/BPS with only IBS), and systemic pain (IC/BPS with IBS plus FM and/or CFS). Of the 207 patients with IC/BPS, 176 could be grouped as follows: 56\% with IC/BPS only, 27\% with regional pain, and 16\% with systemic pain. These 2 studies suggest that the more NBSs used to define the groups, the fewer patients who have only IC/BPS or pelvic symptoms.

**NBSs Associated With Each Other**

By factor analysis, most of the NBSs appear in 4 clusters.\textsuperscript{5} Thus, IC/BPS patients with FM would be more likely to have CFS, IBS, and sicca syndrome than if they did not have FM (cluster 1). Similarly, CPP and migraine appeared together (cluster 2), as did depression and anxiety (cluster 3) and allergy and asthma (cluster 4).\textsuperscript{5} Outside the context of IC/BPS, others have shown similar clusters.\textsuperscript{11,12}

These NBSs have many similarities, other than comorbidity: symptom-based diagnosis, prominent pain in most, overrepresentation in women, normal local histologic findings, nondiagnostic laboratory tests, chronicity, and an unknown etiology. Because of these similarities, FM, CFS, temporomandibular disorder, and IBS are commonly discussed together as functional somatic syndromes (FSSs). CPP and migraine are sometimes included as FSSs, and depression and anxiety are often associated with FSSs.\textsuperscript{13-15} Interestingly, characteristics of IC/BPS are those of the FSSs, suggesting that IC/BPS itself might be an FSS.

**NBSs Precede or Follow IC/BPS**

In 2001, Aaron et al\textsuperscript{18} noted the importance of temporal relationships among unexplained clinical conditions for understanding their pathogenesis.

**NBSs Precede IC/BPS.** Two studies demonstrated that NBSs precede IC/BPS. Wu et al\textsuperscript{19} examined the future probability of an IC/BPS diagnosis in patients with FM, IBS, CPP, or vulvodynia. Groups ranging from 23,000 to 66,000 patients had an ICD diagnosis for each of these syndromes. Those with each syndrome had a significantly greater risk of an IC/BPS diagnosis in patients with FM, CFS, temporomandibular disorder, and IBS which was shorter than IC/BPS with IBS, plus FM and/or CFS, 46\% for CFS, 44\% for depression, 39\% for panic, and 36\% for FM.\textsuperscript{5}

Nickel et al\textsuperscript{6} presented data consistent with NBSs occurring after IC/BPS. The pertinent observation was that the mean duration of IC/BPS occurred in the following pattern: IC/BPS only was shorter than IC/BPS with IBS which was shorter than IC/BPS with IBS, plus FM and/or CFS.

Controls have not been compared; however, integration of 2 studies suggests that the incidence of some NBSs after IC/BPS is likely greater in patients with IC/BPS than in controls. Warren et al\textsuperscript{5} demonstrated that the incidence of NBSs before IC/BPS was significantly greater in those with IC/BPS than in controls. The survey by Clemens et al\textsuperscript{20} reported that in patients with prevalent IC/BPS, one half or more of several NBSs appeared after IC/BPS onset. Linking these data suggests that after IC/BPS onset, patients have a greater incidence of NBSs than do controls.

**Multiple NBSs Increase Risk of IC/BPS**

Two studies have reported that multiple NBSs predict IC/BPS. Warren et al\textsuperscript{5} demonstrated that the number of antecedent NBSs was associated with the risk of IC/BPS\textsuperscript{21} (Table 1). The types of NBSs were skewed, allergy being over-represented in those with few NBSs, and FM, CFS, and IBS in those with many NBSs.\textsuperscript{21} Wu et al\textsuperscript{19} did not present data but stated that “multiple diagnoses of (FM,

### Table 1. Prevalence and odds ratios for IC/BPS stratified by number of antecedent nonbladder syndromes in patients with recent onset IC/BPS and controls

<table>
<thead>
<tr>
<th>NBSs* (n)</th>
<th>Patients (n = 312)</th>
<th>Controls (n = 313)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>22 (7.1)</td>
<td>55 (17.6)</td>
<td>Reference</td>
</tr>
<tr>
<td>1</td>
<td>48 (15.4)</td>
<td>116 (37.1)</td>
<td>1.0 (0.6-1.9)</td>
</tr>
<tr>
<td>2</td>
<td>70 (22.4)</td>
<td>68 (21.7)</td>
<td>2.6 (1.4-4.7)</td>
</tr>
<tr>
<td>3</td>
<td>61 (19.6)</td>
<td>30 (9.6)</td>
<td>5.1 (2.6-9.8)</td>
</tr>
<tr>
<td>4</td>
<td>41 (13.1)</td>
<td>21 (6.7)</td>
<td>4.9 (2.4-10.0)</td>
</tr>
<tr>
<td>5</td>
<td>32 (10.3)</td>
<td>15 (4.8)</td>
<td>5.3 (2.4-11.7)</td>
</tr>
<tr>
<td>≥6</td>
<td>38 (12.2)</td>
<td>8 (2.6)</td>
<td>11.9 (4.8-29.5)</td>
</tr>
</tbody>
</table>

* Eleven antecedent NBSs: chronic fatigue syndrome, fibromyalgia, irritable bowel syndrome, sicca syndrome, chronic pelvic pain, migraine, depression, panic disorder, allergy, asthma, and vulvodynia.
IBS, CPP, and/or vulvodynia) . . . are significant predictors of future IC diagnosis.19

Additionally, 2 investigations report that the prevalence of IC/BPS is greater in those with multiple NBSs than those with fewer. Nickel et al.6 (for the present report) calculated that the odds of IC/PBS increased with increasing numbers of NBSs (Table 2). A Swedish study of >28,000 twins used latent class analysis to group subjects according to 9 symptoms;12 5 classes were identified. The largest had none of the symptoms; 1 class each was characterized by headache, bowel symptoms, and widespread pain. The fifth class had many symptoms; the greatest prevalence of CFS, FM, IBS, depression, and anxiety; and the greatest prevalence of “recurrent urinary problem.”

**HYPOTHESES GENERATED**

We believe that these facts generate ≥5 hypotheses.

Hypothesis 1: NBSs and IC/BPS initiate different processes that lead to different syndromes. The simplest such sequences would be:

a) NBS1→p→IC/BPS,

where p is the process initiated by NBS1 that leads to IC/BPS; and

b) IC/BPS→p′→NBS1,

where p′ is the process initiated by IC/BPS that leads to NBS1.

This reasoning is simple when the link between 2 syndromes is pondered. However, the logic becomes complicated when considering that multiple NBSs precede IC/BPS, and some appear to follow it. In the former situation, each NBS might initiate its own process (p^n) that leads to IC/BPS:

c) NBS1→p^1→IC/BPS,

NBS2→p^2→IC/BPS . . .

NBSn→p^n→IC/BPS.

For the latter, the question is whether IC/BPS initiates a variety of different processes, each of which leads to a separate NBS:

d) IC/BPS→p′→NBS1,

IC/BPS→p^2→NBS2, . . .

IC/BPS→p^n→NBSn.

Factoring in the likelihood that such processes also link many of the NBSs and might diverge from some syndromes and converge on others results in an overwhelming number of possible combinations and permutations.

Hypothesis 2: NBSs and IC/BPS initiate a common process that leads to additional syndromes. This hypothesis can be shown as

e) any NBS→p→IC/BPS,

where p is the common process initiated by each NBS that leads to IC/BPS, and

f) IC/BPS→p→any NBS,

where p is the same process, now initiated by IC/BPS, that leads to any of the NBSs. In this hypothesis, p would be the common pathogenesis of all but the first syndrome and could lead to any other syndrome.

Hypothesis 3: a shared pathophysiology leads to the NBSs and IC/BPS. The simplest, most parsimonious, hypothesis is that the NBSs and IC/BPS all emerge from the same pathogenesis, p. Thus, p would precede the first NBS:

g) NBS1 NBS3 NBS4

NBS2 IC/BPS NBS5

p→-→-→-→-→??

This pre-existence could mean an origin of “p” in genetics or in epigenetic or preceding life events. Small surveys have suggested a genetic predisposition to IC/BPS,22 and the Swedish twin study estimated that genetics accounted for 30% of the variation in the susceptibility to IC/BPS.23 Additionally, the roles of maternal stress in fetal development24 and of early life trauma25,26 on the emergence of IC/BPS have recently been queried.

Hypothesis 4: a pathophysiology common to the NBSs and IC/BPS is found in significantly more patients with many NBSs than in with fewer.

Hypothesis 5: a pathophysiology unique to IC/BPS is found in significantly more patients with only IC/BPS than in with many NBSs.

At first glance, that IC/BPS risk increases with the number of NBSs is not interesting, because it could be explained as the accumulation of risk factors. However, a

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**Table 2.** Prevalence and odds ratios for IC/BPS stratified by number of coexisting nonbladder syndromes in patients with prevalent IC/BPS and controls

<table>
<thead>
<tr>
<th>NBSs*</th>
<th>Patients (n = 205)</th>
<th>Controls (n = 117)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>60 (29.4)</td>
<td>75 (64.1)</td>
<td>Reference</td>
</tr>
<tr>
<td>1</td>
<td>46 (22.4)</td>
<td>28 (23.9)</td>
<td>2.1 (1.2-3.7)</td>
</tr>
<tr>
<td>2</td>
<td>26 (12.7)</td>
<td>9 (7.7)</td>
<td>3.6 (1.6-8.3)</td>
</tr>
<tr>
<td>3</td>
<td>30 (14.6)</td>
<td>1 (0.9)</td>
<td>37.5 (5.0-283.0)</td>
</tr>
<tr>
<td>4</td>
<td>18 (8.8)</td>
<td>4 (3.4)</td>
<td>5.6 (1.8-17.5)</td>
</tr>
<tr>
<td>5</td>
<td>13 (6.3)</td>
<td>0 (0.0)</td>
<td>33.7 (2.0-578.3)</td>
</tr>
<tr>
<td>≥6</td>
<td>12 (5.9)</td>
<td>0 (0.0)</td>
<td>31.2 (1.8-537.7)</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.

Data presented as number of patients, with percentages in parentheses, unless otherwise noted.

Data calculated from Nickel et al.6

* Eight coexisting NBSs: chronic fatigue syndrome, fibromyalgia, irritable bowel syndrome, migraine headache, vulvodynia, tension headache, temporomandibular disorder, and low back pain.

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more engaging conjecture is based on the possible heterogeneity of IC/BPS.

Numerous students of IC/BPS believe the syndrome to be heterogeneous, \textsuperscript{7,27,28} which might mean that it has \( \geq 1 \) pathogenesis. To simplify this discussion, one could assume that IC/BPS has 2 causes. One is a pathogenesis that causes IC/BPS but none of the NBSs. The second causes IC/BPS and, additionally, each of the NBSs. Accounting for age and other factors, one could intuitively conclude that more patients with IC/BPS and many NBSs would have this shared pathogenesis than patients who have IC/BPS with no or few NBSs. This conclusion also can be shown algebraically.\textsuperscript{21} It is intriguing that the classic FSSs of FM, CFS, and IBS were over represented in IC/BPS patients with many NBSs ie, in the subgroup in which a shared pathogenesis could be hypothesized to be most prevalent\textsuperscript{21}.

Additional studies should examine the associations of NBSs with IC/BPS phenotypes. For example, do patients with Hunner’s lesions and inflammation differ in the pattern of associated NBSs compared with patients with normal-appearing bladders and no inflammation?

**Candidate Processes**

Each process (p) denoted in the preceding section is meant to be a series of events that leads to a syndrome. These events could be structural, physiologic, environmental, behavioral, or another type, perhaps occurring in patients with a genetic predisposition. Several pathophysiologies have been shown to accompany these syndromes and thus are candidates for such a process.

**Central Sensitization in Lower Spinal Cord.** Although commonly espoused,\textsuperscript{6,9} central sensitization (CS) at the lower spinal level might not be an important link between IC/BPS and most of its associated NBSs. The clinical data can be interpreted to suggest that CS does not commonly lead to IC/PBS. If it did, the pathophysiology would be that an NBS that includes pelvic pain initiates CS in the lower spinal cord such that the bladder also is perceived as a site of pain. However, this forces the hypothesis that the same process would lead to other pelvic NBSs (ie, that IC/BPS patients with, for instance, CPP would be more likely to have IBS and vulvodynia than IC/BPS patients who did not have CPP). However, in the patients with incident IC/BPS, Warren et al\textsuperscript{5} showed no associations among antecedent CPP, IBS, and vulvodynia.

Nevertheless, 1 NBS after IC/BPS might be explained by CS at the lower spinal level. Warren et al\textsuperscript{29} reported that after the onset of IC/BPS, 23\% of patients noted new symptoms of vulvodynia as a part of their IC/BPS. This would be consistent with sequence b) above in which IC/BPS initiated CS in the lower spinal cord, which resulted in the perception of vulvar pain.

**Systemic Pathophysiologies.** However, the most compelling reason that CS at the lower spinal cord could not be responsible for all the NBSs associated with IC/BPS is that most such NBSs have manifestations well beyond the pelvis. For instance, 1 study revealed that >90\% of patients with IC/BPS had \( \geq 1 \) such NBS.\textsuperscript{5} This observation could be exceedingly important, because it implies that a process outside the pelvis must be responsible for these associations. Several candidates for such a process have been identified and include abnormalities in supraspinal sensory processing, in autonomic function, and in the hypothalamus-pituitary-adrenal axis.\textsuperscript{30}

However, we assume that no single sequence listed in the preceding paragraphs will explain all the associations among the NBSs and IC/BPS, perhaps not even in a given patient. Nature is complicated, and a combination of sequences might be responsible. Furthermore, one could postulate different mediators and modifiers of a given pathogenesis or various triggers to account for the onset of different syndromes at different times.

**TESTING THE HYPOTHESES**

All the facts that generated these hypotheses were revealed in cross-sectional studies of patients with IC/BPS. In searches for pathogenesis, such a design is often frustrating, because the usual residual question is “which came first?” The temporal relationship of a pathophysiology and a syndrome can be particularly vexing because of the difficulty in determining whether the revealed pathophysiology is a cause or an effect of the syndrome.\textsuperscript{18} In the wider field of human chronic pain research, evidence has shown that 1 of the noted candidate pathophysiologies, abnormal sensory processing, can play either role. In patients undergoing thoracic surgery, pre-existing abnormal sensory processing was associated with chronic postoperative pain.\textsuperscript{31} In contrast, in patients with hip osteoarthritis, hyperalgesia at other sites normalized after hip replacement.\textsuperscript{32}

These latter investigations were prospective studies and suggest that such a design will be necessary to identify the temporal relationship of a pathophysiology and IC/BPS. This is because none of the candidate pathophysiologies are assessed in routine clinical practice or have markers that can be appraised retrospectively to discern their times of onset. Thus, additional research of patients with prevalent IC/BPS should be viewed as preparatory to prospective investigations of individuals who have not yet developed IC/BPS.

**Cross-Sectional Studies**

Cross-sectional studies of prevalent IC/BPS would be useful for pathogenesis research if they accomplished 2 tasks in each patient and control: (a) estimating the past sequence of NBSs and, in cases, IC/PBS and (b) assessing present pathophysiologies. Regarding the former, accuracy of syndrome onset could be maximized by the use of personally important dates as chronologic anchors, iterative queries, and medical records.\textsuperscript{5} The participants could then be distributed into subgroups according to types, numbers, and sequences of syndromes.
However, the most critical objective of cross-sectional studies should be to identify the structural, physiologic, environmental, behavioral, genomic, or other processes that distinguish patients with IC/BPS from controls. Included among those that should be sought are the pathophysiologies listed in previous paragraphs. Cross-sectional studies should screen for additional candidate pathophysiologies. The processes more common in patients with IC/BPS would generate the hypothesis that ≥1 preceded IC/BPS and thus would be a candidate for its pathogenesis. Of particular interest would be such studies of patients with recent onset IC/PBS.

**Prospective Studies**

However, to confirm which processes precede IC/BPS and thus might cause it, we believe that a prospective investigation will ultimately be required. The timing of such a study would depend on the confidence of the investigators and sponsors that the cross-sectional studies had identified the important candidate pathophysiologies. A prospective investigation should have these features: restriction to, or powered for, women; the absence of baseline IC/BPS; periodic assessment of candidate pathophysiologies, NBSs, and IC/BPS; and comparisons of those who develop IC/BPS with those who do not. The selection of the sample will dictate the duration, expense, and objectives of the study. The shortest and least expensive would be of women at high risk of IC/BPS (eg, those with multiple NBSs). The longest and most expensive would be of women with neither IC/BPS nor any of the NBSs. Such a study would enroll young women, possibly girls, and might be able to test all the hypotheses, maximizing the opportunities to reveal not only the pathogenesis of IC/BPS, but also the pathogenesis(es) of the NBSs. A study that enrolled women without IC/BPS, regardless of the presence of NBSs, would have possibilities intermediate between these 2 extremes.

**CONCLUSIONS**

NBSs are associated with IC/PBS and with each other and might provide important clues to the pathogenesis of IC/BPS. Additional cross-sectional studies will be useful to generate hypotheses about the pathogenesis of IC/BPS; however, prospective studies will likely be necessary to test these hypotheses.

**References**


