Continence and micturition: physiological mechanisms under behavioral control

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Four different mice
See how they pee
Their urination was studied with zeal
Unfortunately we can’t ask mice how they feel
Because voiding is highly behavior-real
In four different mice

MICE ARE IMPORTANT RESEARCH tools for numerous reasons, including ease of genetic manipulation and breeding. Their use in studying bladder physiology/pathophysiology is well established. However, when one thinks of bladder function purely in terms of urinary storage and elimination, it becomes overly simplistic. The bladder is not an autonomous organ because its function can be volitionally regulated, affected by different behavioral/social situations, and influenced by sex.

Of important historical interest, analysis of male mice voiding behavior using voiding spot assays (VSA) was published in *Science* well over 40 years ago (3). I was fortunate to have met Claude Desjardins, the lead author, when I was a T32-postdoctoral fellow at the University of Virginia in 1995. Male mice were found to void differently based on their social rank (dominant vs. subordinate status). Subordinate males voided less frequently compared with dominant males, when placed together in the same vicinity. This effect of this social stress on male voiding behavior has subsequently been replicated by different investigators (2, 4). Another type of stress, induced by a water avoidance stress test (psychological stress), has been shown to affect female rat voiding behavior (7).

In a study by Bjorling et al. (1) in a recent issue of the *American Journal of Physiology-Renal Physiology*, when VSA were analyzed, a difference between male and female voiding behavior was found in only one of four strains tested. One would have expected consistent differences in all strains. Several possible factors might have mitigated potential differences between the sexes, including lack of resolution of urine spots, duration of testing of only 4 h in the light cycle, and state of hydration of the mice. While this study was not designed to test the replicability of the VSA (which would require more than 2 sites), multiple significant differences were found in the VSA analyses from two different testing sites (Fig. 5A) (1). Whether these differences were a result of the VSA technique and/or an unappreciated difference in animal handling/preparation are unknown. An approach to prevent overlap of urine spots utilized a moving filter paper during the VSA (5).

Use of cystometry to study bladder function is invasive and artificial, compared with the VSA. However, the cystometrogram (CMG) tracings demonstrate bladder pressure-volume relationships which are not possible with the VSA. While the primary design of this study was not to determine the reliability of cystometry performed at different testing centers, it appears that the CMG data were more consistent across the two sites compared with the VSA data (Fig. 5B) (1). Because cystometries were done under anesthesia, this could explain why CMG data were more consistent and also why there was no correlation between cystometries and VSA. Performing mouse cystometry in the awake, freely moving animal has been described (6). Whether cystometry data from awake nonanesthetized animals show more correlation with VSA remains to be seen.

For a bladder to function as it was designed, unlike other organs such as the heart, lung, liver, and kidney, a continual dialogue between it and the nervous system is essential. In humans, normal bladder function necessarily involves psychosocial and behavioral constructs such as socialization, cognition, stress, executive function, and fluid intake behavior. Fortunately, current clinical guidelines already place behavioral modifications (bladder training, prompted voiding, fluid management, biofeedback) as first-line therapy for urinary frequency, urgency, and incontinence. However, a more granular understanding for causes of these bladder symptoms requires murine models. Controlling for psychosocial and behavioral factors shown to affect mice voiding behavior is an important first step in establishing baseline behavior before any interventions to alter continence and/or micturition are applied.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS
Author contributions: T.C.C. drafted manuscript; T.C.C. edited and revised manuscript; T.C.C. approved final version of manuscript.

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