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Reply to: THE CASE AGAINST urethral failure is not a critical factor in female urinary incontinence. Now what? The integral theory system

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We are all indebted to Peter Petros for his role with Ulf Ulmsten in developing the mid-urethral tape. This important advance significantly reduced the morbidity of stress incontinence surgery for women and is now used worldwide. We and our patients owe them a debt of gratitude for this important innovation.

We have been asked to comment on Dr. Petros' recent opinion piece "Urethral failure is not a critical factor in female urinary incontinence"[1] in response to an opinion article that we wrote related to the National Institute of Diabetes, Digestive and Kidney (NIDDK) diseases seminar series on Urethral Function and Failure[2] that brought together experts from around the world. He has chosen to take a debater's stance opposing the idea that urethral function is important to stress, urge, and mixed incontinence. We have recently published a letter to the editor[3] written in response to a paper[4] denying the data that urethral function is the most important causal factor for stress incontinence. Our letter contains rebuttals to the assertion that urethral support is the primary cause of stress continence, which we will not repeat here.

The approach Dr. Petros chooses as a foundation for his "case against" is based on: "Philosophy of science [which] has a number of established and recognized concerns such as examining the basis of rational theory preference and the nature of explanation… the epistemological importance of the institutions, practices and ethos that regulate the logical soundness of the debate in which scientists evaluate theories."

We lack training in either debate or the philosophy of science and will not comment on that. However, we did learn the essential elements of the scientific method: observe, theorize, hypothesize, test the hypotheses with experimental measurements, and accept or refute. Dr. Petros has observed and theorized. However, we have not been able to find hypothesis-testing measurements that compare findings in symptomatic women compared with normal asymptomatic volunteers to support his argument.

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Much of his argument rests on the results of surgery. These are, of course, unreliable to confirm a theory. In 1914, Howard Kelly[5] used the success of his operation to tighten the vesical neck sphincter area by plication to "prove" that weak vesical neck closure was responsible for stress incontinence. About a decade later, Victor Bonney came to a different conclusion from success of the same operation, saying that Kelly used fascial stitches to close the dead space and therefore supported the urethra—proving that urethral support was the cause.[6] Thus, the same operation was used to support completely opposite conclusions. The fallibility of using surgical results as proof are obvious. They could, for example, "prove" that obesity is caused by an enlarged stomach since reducing stomach size with bariatric surgery results in weight loss. Or that ulcers are caused by gastric acidity (not *Heliobacter pylori*) because excision of the acid-producing part of the stomach reduces ulcers. There is no question that the mid-urethral tape stops stress incontinence in most stress incontinent women, but this is not enough for proof.

The mid-urethral tape operation, performed by some of the nation's best surgeons in the NIH Urinary Incontinence Treatment Network, has a 20% objective failure rate and 40% subjective cure rate.[7] Because this and other support operations do not change maximal urethral closure pressure (MUCP), this should not be a surprise to anyone.[8] There is strong evidence that the primary cause of stress incontinence is urethral failure and that can explain imperfect results from urethral support operations.

Table 1 summarizes hypothesis-testing evidence proving the importance of deficient urethral function in stress incontinence and the fact that it is more strongly predictive than urethral support parameters. These hypothesis-testing studies compare MUCP and urethral support in women with symptomatic demonstrable stress urinary incontinence (SUI) to normal volunteers of similar age, parity, and hysterectomy status who were demonstrably continent. We report the differences as effect sizes because that statistic allows the difference between two groups to be quantified even though they are made in different units (e.g., cm H_2O for MUCP and mm for urethral support).

These studies were undertaken to see what it was about urethral support that was most important to stress incontinence, not because we thought at the time that urethral function was most important. To be honest, this line of investigation was not undertaken to find differences in urethral function. It was conducted to test the Hammock Hypothesis,[12] to measure differences in urethral support structures between cases and properly matched asymptomatic controls, and to look at what specific damage to the anatomical components of the urethral support system differed between the groups. At that time, Dr. Petros and I (DeLancey) basically agreed on the concept of support. This Hammock Hypothesis was based on observations of the anatomical support system in dissection[13] and direct observation in the operating room during 71 retropubic operations, where the support structures could be directly observed.[14] These observations suggested that the support system was defective. We sought to test the hypothesis using ultrasound and MRI so that controls could be observed while keeping other possibilities in mind. Having spent 15 years prior to testing the hypothesis and writing about urethral support, it was not without considerable pain that I was forced to accept the reality of our findings that urethral support was not the dominant factor (DeLancey). Yet the data were clear—an example of Huxley's

observation: “The great tragedy of Science—the slaying of a beautiful hypothesis by an ugly fact.”[15]

The case for suggesting that urethral function plays a role in urge incontinence comes from a population-based study that included a group of women with urge incontinence in addition to those with stress incontinence.[11] White women with urge incontinence had MUCPs that were 21% lower than White controls on average—just as low as White women with stress incontinence. Interestingly this was not true for Black women with urge incontinence. The fact that Black women were only half as likely as White women to have incontinence of any type was consistent with the fact that their urethras were 22% stronger on MUCP on a population basis. The population-based questionnaire section of this project included 2,000 Black and 1,000 White women and was performed by the prestigious Institute for Social Research. This section included demographics, health history, lifestyle factors, and urinary incontinence experience. None of these factors explained differences in prevalence of stress or urge incontinence between Black and White women; only MUCP measured in a urodynamic subsample of 400 women selected with and without incontinence did.[16]

Of course, urethral support does play some role in stress incontinence; we have never denied that. However, and this is the important point, it was *not* the primary factor. It’s not even close in the typical mid-life woman presenting for care—the most important group to consider. We were surprised with this finding and sought other ways, unsuccessfully, to determine what aspect of support was responsible.[17] The rapier-like yet deceptively simple question posed by our statistician Ken Guire is: “Tell me, John, why didn’t anyone think the sphincter was important to urine leakage?”

Now, let’s review how this satisfies the scientific method. We observed, hypothesized, tested the hypothesis with measurements in women with stress and urge incontinence, and repeated this several times. We found the same results. In multivariable modeling of over 200 women, after adjusting for body mass index, the MUCP alone correctly classified 50% of cases. Adding the best predictors for urethrovaginal support and cough strength to the model added 11% to its predictive ability.[10] Similarly, in de novo stress incontinence (n=80) compared to primiparous controls of equal age, parity, and time from delivery (n=80), 25% was explained by MUCP and only an additional 12% by support loss.[9] Although the findings that women with urge incontinence have similar urethral failure have not yet been repeated, that work is underway through the Lower Urinary Research Network sponsored by the NIDDK.

Why do so many people still believe it is lack of urethral support that causes stress incontinence? Well, isn’t it what everyone believes? Of course, it is an attractive hypothesis to surgeons who would like to believe they are addressing the cause of a problem rather than just doing a compensatory operation that works. They see in their patients that they put a tape at the mid-urethra and stress incontinence goes away. I believed that for 25 years (DeLancey).

So why does this matter? There are well over 250 operations that have been described for the treatment of stress incontinence, the vast majority of which seek to alter urethral support. Well-conducted studies still show a significant proportion of women with persistent stress.

This therapeutic target of urethral support is overcrowded—250 different operations in an area the size of a shot glass! However, urethral failure is a long-neglected therapeutic target. We call attention to the importance of urethral function to stimulate researchers to explore why women have poor urethral function, how failure can be identified and prevented, and what might be done to improve it. Until we recognize its importance—and study and innovate in this domain—treatment success is likely to stagnate.

As the revolutionary economist, John Maynard Keynes observed: "The difficulty lies not so much in developing new ideas as in escaping from old ones."[18] It's time to move forward based on evidence.

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Table 1.

Summary of studies comparing MUCP and urethral support in women with SUI and asymptomatic women volunteers group-matched for age and parity

Study	SUI (n)	Controls (n)	% Reduction in MUCP in Cases Compared to Controls[a]	MUCP Effect Size	Support Effect Size
SUI 9-months after birth[9]	80	80	25%	0.9	0.76
Symptomatic SUI[10]	103	108	41%	1.5	0.45
Population-based[11]	102	132	21%	0.5	NS

[a]All group comparisons statistically significant

Abbreviations: SUI, stress urinary incontinence; MUCP; maximal urethral closure pressure; NS, not significant