Annals of Internal Medicine

COMMENTS AND RESPONSES

John Loesch and Harry Goldblatt: Two Great Pioneers in Circulation Research

TO THE EDITOR: Glodny and Glodny (1) state that first John Loesch and then our father, Harry Goldblatt, published papers with the same “central proposition”: “Renal ischemia causes persistent hypertension.” They also state that because of the “primacy” of his observations, Loesch should be recognized as the “discoverer of renovascular hypertension.”

Earlier, Theodor Fahr suggested that “renal ischemia, by itself, may play an important part in the development of the hypertension that is associated with more or less diffuse vascular disease in man” (2). Several investigators who preceded both Loesch and Goldblatt deliberately interfered with the renal circulation, injuring the kidney, with some success in producing hypertension (2).

Priority of publication, however, is irrelevant. The Glodnys’ term “Loesch–Goldblatt experiments” inappropriately joins the names of 2 independent investigators whose aims, experimental methods, and results were fundamentally different.

Loesch investigated the hypothesis that vasospasm causes human hypertension. His model involved intermittent cross-clamping of the renal pedicle. His hypothesis remains unproved, and his findings have not been reliably replicated. Goldblatt, who observed the high correlation between intrarenal vascular disease found at autopsy and “essential” hypertension—hypertension without obvious renal origin—during life, hypothesized that intrarenal vascular disease causes benign human essential hypertension. By persistently constricting the renal artery of the dog, he produced sustained hypertension that closely resembled the human disorder. His technique and results have been replicated throughout the world.

Loesch reported that intermittent clamping of the pedicle of a dog’s kidney explanted beneath the skin caused sustained hypertension. Goldblatt repeated Loesch’s work with the kidney in situ and in a way that avoided compressing the ureter and renal vein with the artery. He demonstrated that intermittent occlusion of the renal artery does not produce elevation of the blood pressure (3). Even Loesch’s mentor, Dr. Frederick Allen, an outspoken critic of Goldblatt, admitted that “[o]nly exceptional dogs develop hypertension with the number and duration of clampings which Loesch describes” (4).

The parenchymal injury that Loesch produced included “necrosis with consequent inflammation.” Loesch called his model “experimental nephritis.” Findings in the urinary sediment in 5 dogs (microscopic hematuria from the first clamping onward and, in 2 animals, “abundant red and white blood corpuscles”) suggested that “nephritis” was an appropriate term (5). The Glodnys omit this information.

Goldblatt’s model conformed to the characteristics of benign human essential hypertension and differed from preceding models, including Loesch’s model, in which animals that developed hypertension usually died early because of renal insufficiency. Hypertension of this type resembles that of glomerulonephritis—the renal origin of which has never been seriously questioned since the time of Richard Bright. With the publication of Goldblatt’s work, a century after Bright’s work, the paradigm shifted.

The Glodnys assert that Goldblatt did not test the efficacy of his technique when he disproved Loesch’s findings. That testing and its results are detailed in Goldblatt’s paper (3). The Glodnys state that “Goldblatt finally acknowledged that Loesch had succeeded in inducing ischemia and that Loesch had produced chronic, sustained hypertension. He stated, ‘The positive results obtained by Loesch . . . may well have been due . . . to . . . renal ischemia.’” So, in the end, Goldblatt acknowledged that Loesch had produced sustained hypertension by renal ischemia” (1). However, Goldblatt’s actual statement is as follows: “The positive results obtained by Loesch in the other two dogs may well have been due to persistent [and unintended] constriction, of lesser degree, of one or all of the components of the renal pedicle, with resultant persistent renal ischemia” (3). Goldblatt had explained why Loesch failed to prove his hypothesis. By omitting “persistent” from both sentences, the Glodnys completely pervert Goldblatt’s conclusions.

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References


IN RESPONSE: We thank the Goldblatts for their letter and appreciate their interest, and we would like to respond to their comments.

Harry Goldblatt did not mention that the conclusions of his own work presented in 1934 had been reported previously. For this reason, we believe that John Loesch did not receive due recognition until he was recalled by us.

The Goldblatts cited Fahr using their father’s article. Indirect quotation may result in changes, as in the case of P.J. Goldblatt’s statement on the lecture of 1932 (1). Loesch’s article is actually in 3 parts. Loesch was familiar with Volhard’s vasospasm hypothesis, but he did not test it (2, 3). Goldblatt and Loesch both realized that they could generate persistent hypertension by means of ischemia, and both of them rightly received recognition for this. Loesch stated very clearly that he did not occlude the ureter. To prevent uremia, he successfully varied the occlusion intervals and, thus, the extent of ischemia. He was, therefore, able to extend the animals’ lives, and this fact should be acknowledged. Goldblatt also had to deal with the problem of animals dying due to uremia. Goldblatt, in contrast to Loesch, did not examine the urine sediment.

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At least 2 different “Goldblatt models” are known. We believe it would be appropriate to call them “Loesch–Goldblatt models,” because Goldblatt had not yet fully realized the difference between the 2 models in 1934. The “one kidney–one clip model” in a rabbit, for example, does not exhibit “the characteristics of benign human essential hypertension” because these animals die of malignant hypertension after a few weeks (4).

The Loesch–Goldblatt models still puzzle us, but a solution to one of the greatest puzzles is now imminent: The structures of the lipid antihypertensive hormones, the “medullipins” and “angiolysins,” which are released by the kidney into the bloodstream after “unclipping” or when perfusion pressure is increased (4), will be elucidated shortly. These are among the most potent antihypertensive agents and vasodilators known (5, 6). The means of achieving this are now available (5, 6). The paradigm will shift once more, and we will again remember 2 great researchers: Harry Goldblatt and John Loesch.

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References

TO THE EDITOR: Brown and colleagues (1) evaluate the diagnostic accuracy of the 3 Incontinence Questions (3IQ) for discriminating between types of urinary incontinence and suggest that the questionnaire may be used to classify and treat women with urinary incontinence in the primary care setting. The data from the study, however, indicate that the authors’ confidence in the 3IQ is misplaced. We can interpret the results of the study by using likelihood ratios to compute posttest probabilities (predictive values). With the extended evaluation as the reference standard, the prevalence (pretest probability) of urge incontinence in the study was 39% (119 of 301 patients). For classifying urge incontinence, the 3IQ generated a positive likelihood ratio of 3.29 (95% CI, 2.39 to 4.51) and a negative likelihood ratio of 0.32 (CI, 0.23 to 0.43). When a woman’s response to the 3IQ was positive, the probability that she has urge incontinence is 68% (CI, 59% to 76%, (computed by using the formula: pretest odds X positive likelihood ratio = posttest odds).

Similarly, the prevalence of stress incontinence in the study was 44% (132 of 301 patients). For classifying stress incontinence, the 3IQ generated a positive likelihood ratio of 2.13 (CI, 1.71 to 2.66) and a negative likelihood ratio of 0.24 (CI, 0.15 to 0.36). When a woman’s 3IQ response is positive, the probability that she has stress incontinence is 62% (CI, 55% to 69%, When a woman’s 3IQ response is negative, the probability is 16% (CI, 10% to 23%).

Clearly, a test that misclassifies two thirds of women with urge incontinence and three fifths of women with stress incontinence would have limited application in clinical practice. This is not surprising because the likelihood ratios of 2.0 to 5.0 and 0.5 to 0.2 have been shown to generate small changes in the probability of the target disorder (2). The test properties (positive likelihood ratio) of the 3IQ cannot make large and clinically meaningful shifts between pretest and post-test probabilities and may not help physicians in determining the type of urinary incontinence. I would urge caution in using the 3IQ for distinguishing types of urinary incontinence in the primary care setting.

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Potential Financial Conflicts of Interest: None disclosed.

References

TO THE EDITOR: I read Brown and colleagues’ paper (1) with great interest. The proposed 3IQ test will certainly aid physicians in their work-up of women with urinary incontinence. I have 2 questions or suggestions to further improve the accuracy of this test and its applicability in practice.

My first issue involves the intended use of the 3IQ test. The study population included women with at least 3 episodes of urinary incontinence per week for 3 months or longer. The authors repeatedly state that the 3IQ test is to be applied as a diagnostic tool to distinguish between urge and stress incontinence in women with urinary incontinence. It is, thus, not supposed to be a screening tool to detect cases of (any type of) urinary incontinence in women in the general population. Given this, I do not understand the first question of their questionnaire, which rather addresses screening or case finding than diagnosis. Is the 3IQ test meant to be a diagnostic test for women with not-yet-established urinary incontinence (in which case, the first question is redundant and even misleading) or a screening test? I would urge caution in using the 3IQ for distinguishing types of urinary incontinence in the primary care setting.
My second issue concerns the value of the 3IQ test in combination with other tests. The authors focused on the accuracy of the 3IQ test in isolation. This single-test approach is, indeed, prevailing in the medical literature. But interest for a multivariable approach in diagnostic research is increasing (2, 3). Such a multivariable approach allows investigators to estimate the added value of a test beyond other tests, provides results that are commonly more relevant to practice (hardly any diagnosis is based on a single test), and may also improve the accuracy and applicability of a test. Brown and colleagues documented various other patient characteristics that are known—from their own previous research (4)—to be related to the presence of either stress or urge urinary incontinence, including race, body mass index, diabetes, parity, and hysterectomy. They could easily undertake a multivariable analysis (for example, logistic regression) or another type of subgroup analysis to provide insight in the diagnostic accuracy of the 3IQ test in relation to these other characteristics. Such analysis would result in a more targeted use of the 3IQ if, indeed, the test’s accuracy does differ across these relevant patient subgroups.

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Potential Financial Conflicts of Interest: None disclosed.

References

TO THE EDITOR: I disagree with Brown and colleagues’ conclusions in their study (1) on the use of the 3IQ test to diagnose and treat urinary incontinence. I recommend against implementing this technique in primary care.

Their use of an extended evaluation as the gold standard for determining the type of urinary incontinence is not the accepted standard for such research. Although urodynamic studies are not justifiable as routine testing in all urinary incontinence, they are the accepted gold standard for research (2). Therefore, Brown and colleagues’ estimates of sensitivity and specificity cannot be considered accurate.

The generalizability of the 3IQ test to internal medicine practice is not assured because Brown and colleagues excluded patients of a more advanced age and patients with neurologic disorders.

The recommendation to use 3IQ to direct nonspecialist care of urinary incontinence underemphasizes the potential harm of antimuscarinic agents in treating urge incontinence. While mentioning the risk for urinary retention as a minor concern in treating misclassified patients, the authors did not consider the central nervous system adverse effects of cognitive impairment and delirium. They also did not consider gastrointestinal adverse effects, such as reflex esophagitis and constipation.

Diagnosing and treating urinary incontinence on the basis of the 3IQ would include prescribing potentially harmful medications to patients without an indication up to 23% of the time. While this may serve the financial interest of the sponsor of the study (manufacturer of solifenacin succinate), it cannot be considered evidence-based practice.

An evidence-based primary care approach to diagnosing urinary incontinence is presented in the second edition of Diagnostic Strategies for Common Medical Problems (3). The in-press third edition (4) will further emphasize the need, and means, for an acceptable diagnosis so that treatment can be based on the best evidence and the appropriate thresholds of certainty and risk. Questionnaires can establish the presence of incontinence, but when compared with an appropriate gold standard test, they cannot differentiate the type with enough accuracy to direct drug treatment.

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Potential Financial Conflicts of Interest: None disclosed.

References

IN RESPONSE: We appreciate the opportunity to respond to the comments by Drs. Kalantri, Moons, and Rich. We agree that the accuracy of the 3IQ is modest. However, Dr. Kalantri considerably overstates the proportion of women with urge incontinence (43%, which is not two thirds) and stress incontinence (23%, which is not three fifths) who are misclassified by the 3IQ (see our Table 3). As we stated in our conclusions, the modest accuracy of the 3IQ is acceptable given that the risk for misclassification and inappropriate treatment by primary care is low.

In response to Dr. Moons, the 3IQ is meant to be a diagnostic test applied in women with urinary incontinence and is not meant to be a screening tool for case finding. We included the first question of the questionnaire because some women may have incontinence that occurs less than monthly, and current incontinence in the last 3 months seemed a reasonable threshold for continuing onto the next 2 questions to determine the type of incontinence.

No gold standard test is agreed upon. To determine the gold standard, we consulted with international experts and our investiga-
tors and did a literature review. We respectfully disagree with Dr. Rich’s conclusion that urodynamics are required for the gold standard. For clarification, we did not exclude older participants (age range for participants in the Diagnostic Aspects of Incontinence Study [DAISy] was 40 to 94 years) and we excluded only patients with major neurologic disease. We contend that our cohort was, in fact, very generalizable to patients who should be treated by primary care.

We agree with Dr. Moons that prediction based on several risk factors might, in principle, outperform our assessment essentially on the basis of 2 questions. However, the risk factors that he cites from our earlier work are considerably more useful for predicting weekly incontinence rather than for classifying type of incontinence among women who are known to have it. In addition, more complicated diagnostic algorithms are less useful in primary care practice.

We suggest using a self-help booklet as the first line of treatment (1). We agree with Dr. Rich that further studies of adverse effects of medications for urge incontinence should be conducted to evaluate the effect on cognitive functioning. We also recommend further study to determine the clinical outcomes that would result from using the 3IQ.

Until those studies are performed, using the 3IQ in a primary care setting seems reasonable.

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Reference

CORRECTIONS

Correction: Narrative Review: Electrocution and Life-Threatening Electrical Injuries
In an article on electrocution and life-threatening electrical injuries (1), current was defined incorrectly. Current (measured in amperes) is the flow (or flow rate), not the amount, of electrons. The unit of quantity or amount of electrons (or electric charge) is the coulomb. Thus, a coulomb is the amount of electric charge as a result of a current of 1 ampere flowing for 1 second.

It should be also noted that although direct current can be used for power transmission (particularly at extremely high voltage), most power transmission lines in the United States are alternating current.

Reference

Correction: Update in General Internal Medicine
In the recent Update in General Internal Medicine (1), the age of participants screened in the IDEAL (Incremental Decrease in End Points Through Aggressive Lipid Lowering) study was reported incorrectly. The IDEAL study screened 9868 patients who were 80 years of age or younger.

Reference

Correction: The Association between Common Vitamin D Receptor Gene Variations and Osteoporosis
In a recent meta-analysis on the association between vitamin D receptor gene variations and osteoporosis (1), an author’s name was misspelled. The twelfth author’s name is Antonietta Amedei, not Amidei.

Reference

Correction: Discordance between Sexual Behavior and Self-Reported Sexual Identity
In a recent article on sexual behavior and self-reported sexual identity (1), the following disclaimer was omitted: “The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.”

Reference