

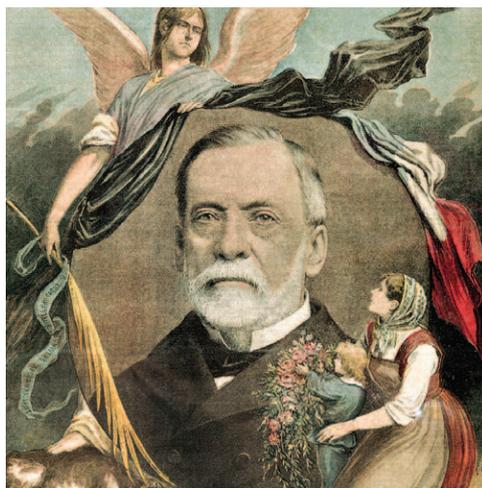
# The Scientific Journey to Predicting and Preventing Postoperative Pain

## Recalling Dr. Wall's Stories along the Way

**M**ODERATE or severe acute postoperative pain, and the transition to chronic pain in some patients, cannot currently be predicted or prevented. In clinical practice, daily exposure to these conditions and their ill-defined etiology conspire to gradually instill an acceptance of these outcomes as unavoidable. We place them in an entirely different category than preventable outcomes such as postoperative infection, forgetting that until the mid-19th century postsurgical infection was also believed to be inevitable.<sup>1</sup>

The kind of large-scale, rigorously executed, prospective, longitudinal study that serves as the basis of the reports by Kaunisto *et al.*<sup>2</sup> and Kambur *et al.*<sup>3</sup> in this issue of *ANESTHESIOLOGY* constitutes a critical component of the research needed to also move postoperative pain from inevitable to routinely preventable. The authors are to be congratulated for successfully consenting and enrolling study participants during a challenging time in their lives between breast cancer diagnosis and surgery, performing preoperative psychophysical testing, and administering a standardized anesthetic regimen and detailed postoperative pain assessment and opioid treatment protocol. The amount of time, effort, and dedication necessary to complete such a study cannot be overstated.

Using data from this study, Kaunisto *et al.*<sup>2</sup> evaluated preoperative phenotypic and psychophysical predictors of acute postoperative pain and found that the preoperative psychophysical assessments performed were only weakly correlated with acute postoperative pain and oxycodone consumption. Phenotypic factors assessed, including age, type of surgery, and preoperative anxiety, together explained only approximately 16% of interindividual variation in



***“As demonstrated by the example of postoperative infection, the unavoidable outcome of today can become the preventable outcome of tomorrow.”***

work to propose that postinjury pain must be considered in the context of, and as only one manifestation of, a well-choreographed, time-dependent, integrated physiologic response designed to optimize the likelihood of surviving a life threat. Consistent with Dr. Wall's hypothesis, subsequent decades of research have elucidated mechanisms by which the activation of neurobiological stress system such as catecholaminergic and endogenous opioid systems and the hypothalamic–pituitary–adrenocortical axis exert time-dependent effects on memory (*e.g.*, see study by Diamond *et al.*<sup>5</sup>), psychological responses (*e.g.*, see studies by Pitman *et al.*<sup>6</sup> and McEwen *et al.*<sup>7</sup>), pain processing (*e.g.*, see studies by Le Roy *et al.*,<sup>8</sup>

oxycodone consumption. Kambur *et al.*<sup>3</sup> evaluated the association between genetic variants in the gene catechol-*o*-methyltransferase and preoperative psychophysical predictors and acute postoperative pain and oxycodone consumption and found no significant associations. Although the findings reported in these two studies advance the field, the results are somewhat limited given the size of the cohort and rigor of the data collection.

In the design and/or analysis of future cohort studies of persistent postoperative pain, several points may be worth mentioning. These points flow primarily from a conceptualization of postinjury pain proposed in a delightful and insightful essay written more than 30 yr ago by Patrick Wall.<sup>4</sup> In this essay, Dr. Wall<sup>4</sup> drew upon both his personal experiences (including those with wounded deer and his injured dog) and his professional

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◆ This Editorial View accompanies the following articles: Kaunisto MA, Jokela R, Tallgren M, Kambur O, Tikkanen E, Tasmuth T, Sipilä R, Palotie A, Estlander A-M, Leidenius M, Ripatti S, Kalso EA: Pain in 1,000 women treated for breast cancer: A prospective study of pain sensitivity and postoperative pain. *ANESTHESIOLOGY* 2013; 119:1410–21; and Kambur O, Kaunisto MA, Tikkanen E, Leal SM, Ripatti S, Kalso EA: Effect of catechol-*o*-methyltransferase-gene variants on experimental and acute postoperative pain in 1,000 women undergoing surgery for breast cancer. *ANESTHESIOLOGY* 2013; 119:1422–33.

Ballina *et al.*,<sup>9</sup> and Joly *et al.*<sup>10</sup>), wound healing (*e.g.*, see study by Vileikyte<sup>11</sup>), and metabolism (*e.g.*, see study by Marcovechio and Chiarelli<sup>12</sup>) in a time-dependent and sometimes sex-dependent (*e.g.*, Devall *et al.*<sup>13</sup> and Bortsov *et al.*<sup>14</sup>) manner.

One concept which may be deduced from this work is that, because of the protean influence of stress system effectors and their powerful effects on pain processing after injury/life threat, preoperative factors that provide a summary evaluation of the phenotypic effects of these systems (*e.g.*, psychological factors, cognitive factors, and previous pain) are more likely to effectively summarize biologic vulnerability to postoperative pain and predict postoperative pain outcomes than psychophysical assessments which evaluate more isolated aspects of physiology. Another ramification of considering postoperative pain from this conceptual perspective is that predictive models assessing stress-related biologic factors with protean effects should avoid putting other characteristics influenced by this factor as covariates in a predictive model, least the biologic effect of the factor be adjusted out: for example, in the study by Kambur *et al.*,<sup>3</sup> models evaluating the potential influence of catechol-o-methyltransferase genotype on phenotypic outcomes adjusted for anxiety, body mass index, and risk of chronic pain, yet catechol-o-methyltransferase genotype has been shown to influence each of these factors (*e.g.*, see studies by Kring *et al.*,<sup>15</sup> Montag *et al.*,<sup>16</sup> and Diatchenko *et al.*<sup>17</sup>). Excluding such factors in this particular analysis may have had no effect, but in general not considering the pleiotropic effects of stress-related biological factors in prediction models of postoperative pain is likely to increase the risk of type II error.

As mentioned above, stress-related biologic factors influencing postoperative pain are likely to be time and/or sex dependent. In addition, genes with an important influence on stress systems critical to survival may have potentially counter-balancing genetic variants across the gene. Because of these characteristics, the influence of stress-related genes on pain outcomes may frequently only be identified *via* analyses that account for these complex interactions.<sup>14</sup> The assessment of interactions is particularly power dependent; therefore, methods that maximize power and optimally balance the risk of type I and type II error are important. In this regard, it may be most useful in studies evaluating postoperative pain to focus on pain severity rather than opioid consumption because opioid consumption depends not only on pain intensity but also on an individual's willingness to use opioids for their pain, their metabolism of opioids, and/or their vulnerability to and tolerance for opioid side effects. Also, in performing genetic analyses, a Bayesian approach in which tiered genetic analyses are performed based on pretest probability is sometimes used (*e.g.*, see study by Smith *et al.*<sup>18</sup>) and has substantial theoretic appeal to maximize power. In this approach, the subset of genetic variants with the highest pretest probability of association (based on available evidence) are tested first, and statistical adjustment for multiple comparisons is made based on the number of tests

in this group only. (Often this group of single-nucleotide polymorphisms accounts for only a small proportion of the overall single-nucleotide polymorphism pool.) Then the remaining larger pool(s) of single-nucleotide polymorphisms is/are evaluated, with additional adjustment for multiple comparisons among the larger subsequent tier or tiers more appropriately aligning pretest probability to significance level.

As demonstrated by the example of postoperative infection, the unavoidable outcome of today can become the preventable outcome of tomorrow. The performance of large-scale, prospective studies such as those performed by Kaunisto *et al.*<sup>2</sup> and Kambur *et al.*<sup>3</sup> is critical to this scientific journey. Along the way, we would do well to remember Pat Wall's stories of his injured dog and his encounters with wounded deer in the New England woods.

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## ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

### “I Awaken to Glory”



This lovely work of art replaced the second of the two side relief sculptures stolen in the 1980s from the Horace Wells Memorial at Hartford's Cedar Hill Cemetery. This south-facing replacement bronze (*left*) was cast by sculptor Anatoly Mikhailov. Beneath the waking woman (*right*) he cast the phrase: “I Awaken to Glory.” Opening around her with the dawning day are flowering morning glories. Both of Mikhailov's sculptures—this one and the north-facing “I Sleep to Awaken”—memorialize nitrous oxide pioneer Horace Wells. (Copyright © the American Society of Anesthesiologists, Inc.)

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