EDITORIAL

The positives of a negative study

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Dr. Gerald Tuite and his colleagues at Johns Hopkins All Children's Hospital in St. Petersburg, Florida, have submitted an important study⁶ demonstrating the lack of efficacy of the controversial Xiao procedure—a somatic-to-autonomic nerve transfer for improving bladder function—in children with myelomeningocele (MM) or lipomyelomeningocele (LMM). The study represents one of the few prospective randomized trials not only in pediatric neurosurgery, but also in neurosurgery in general. Beyond the surface reporting of an ineffectual surgical procedure, this study by Tuite et al.⁶ sheds light on many other salient topics related to clinical research, including ethics, scientific misconduct, scientific integrity, and the virtues of a “negative” study, which are just as impactful as its more evident primary outcome. The authors should be commended for this important work.

The Xiao procedure has received much attention from desperate parents of children with MM/LMM, pediatricians, urologists, and the lay press. Its fanfare extends beyond the field of neurosurgery. But was all this fanfare merited? The present well-executed study,⁶ along with the authors' prior work,⁷ contradicts widely cited studies^{4,5} that were reported to validate the efficacy and safety of the Xiao procedure. Perhaps a little more history about the inventor of the Xiao procedure is needed to put the current study in context and highlight why it is so significant. Interestingly, Dr. Chuan-Guo Xiao, a urologist and founder of the self-named Xiao procedure, is himself a polarizing figure.

Dr. Xiao conceived the idea for an innovative surgical procedure to restore bladder function in patients with MM, LMM, or spinal cord injury while working in the US under a National Institutes of Health grant in the late 1980s. In 1995 Xiao returned to China to perform clinical studies designed to demonstrate the efficacy of his newly described Xiao procedure. He benefited from the regula-

tory environment that governs China's large health care market and human experimentation. Through his own publications,^{8–13} Dr. Xiao claimed a 70%–90% rate of success in restoring bladder control. Yet these astonishing results have not been duplicated by any center outside of China. The zenith of Dr. Xiao's career was the opening of a private hospital dedicated exclusively to performing this procedure. He capitalized on medical tourism, where despairing foreigners, including Americans, would pay out of pocket to have this procedure performed. Unfortunately, the rest of his professional career and life plays out like a soap opera. In 2010, Dr. Xiao was accused and then arrested and convicted of hiring thugs to attack critics of his procedure, doubters of his academic credentials, and whistleblowers of research fraud and fabrication of data.³

Dr. Xiao was sentenced to five and a half months in prison. Since then, his voice may have been silenced, but his infamous legacy lives on. Since 2010, more than 250 patients in China who claim that the Xiao procedure does not work³ have been threatening further civil and criminal legal action against hospitals or Dr. Xiao directly. Moreover, there have been serious complications related to this procedure involving the sacrifice of functioning ventral nerve roots and subsequent loss of motor function.^{4–7}

“Scientific integrity” encompasses a broad spectrum of responsibility, which includes deterring plagiarism, prohibiting the falsification of scientific data to support a priori conclusions (e.g., studies associating autism with vaccines), requiring full disclosure of all potential areas of bias (e.g., the initial clinical studies investigating the safety and efficacy of bone morphogenetic protein [BMP], for which authors failed to disclose significant financial relationships with the manufacturer of one form of BMP), curtailing scientific misconduct, and the mandate of editorial boards of scientific medical journals to publish high-quality science.²

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Furthermore, there are too many “pay-to-publish” journals where the rigor of the peer-review process and quality control is questionable. At times, authors need to realize and accept that their work may not be suitable for publication as composed and that further work to improve or validate the message would be of benefit. A system must be put in place that properly monitors fraud and plagiarism, checks reasonable allegations and prosecutes libelous ones, and protects whistleblowers. The careers of clinicians and scientists, the future of the scientific method, and most importantly, the health, well-being, and lives of our patients are at stake.³

Lastly, I would like to make some brief comments on the positive aspects of a “negative” study. Significant author, editorial, and publisher biases exist toward publishing only studies that report positive results, where a hypothesis is confirmed and further research is inspired. On the contrary, there are likely many more studies that produce nonconfirmatory or negative, observations that refute current ideas or carefully constructed hypotheses, such as the present study.⁶ These negative studies—arguably even more valuable in science—are an integral part of scientific progress and deserve more focus.¹ Obvious benefits of publishing negative results include reductions in duplicated efforts between various research groups; revelations of fundamental flaws in commonly used methods, drugs, or reagents; acceleration of the cycle of scientific progress; and the promotion of a culture of robustness, transparency, and openness, the noblest aspect of science.¹ The reality of science is that it is untidy, complex, confusing, and imperfect; negative studies are the essence of the reality of science. A quote by Jules Verne, famed author and ostensibly the father of science fiction, summarizes my thoughts about negative studies: “Science, my lad, is made up of mistakes, but they are mistakes which it is useful to make, because they lead little by little to the truth.”

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Disclosures

The author reports no conflict of interest.