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Commentary

Translational research in pediatric pain: A new frontier

Christine B. Sieberg

It was the Spring of 2011 and I was in the process of transitioning from being a postdoctoral fellow to an attending psychologist in the Pain Treatment Service at Boston Children's Hospital. I had learned a great deal about treating complex, treatment refractory chronic pain in children during my fellowship. After all of the years of schooling and training, I was excited to become an independently functioning psychologist. Better still, I would be serving as an attending at the Mayo Family Pediatric Pain Rehabilitation Center (PPRC), a renowned day hospital program for youth with chronic pain and disability. Having devoted time during my fellowship at the PPRC, I knew firsthand how rewarding the work was – children come in with debilitating chronic pain and disability and for the most part, after 3 to 5 weeks of intensive physical and occupational therapy, along with psychological treatment and medical support, they get better, and they skip, run, and dance out of the program ready to pick up where they left off before chronic pain consumed them. Our treatment outcome research confirms the efficacy of this program (Logan et al., 2012a,b).

While this was all wonderful, I was left wondering, how do these children end up like this? How do they go from living their lives to not being able to cope and function? Many of our patients have missed months and in some cases years of school. They no longer see friends or engage in recreational and leisure activities, with many struggling to complete activities of daily living. As one patient of mine stated "I don't have the strength to get to the bathroom". On top of this the children and parents often present in significant psychological distress. As a psychologist, I am keenly aware of how psychosocial variables such as anxiety (Simons et al., 2012), fear of pain (Simons et al., 2011), catastrophizing (Caes et al., 2011), and parental distress and responses to child pain (Claar et al., 2008; Sieberg et al., 2011; Vervoort et al., 2011) contribute to the maintenance and exacerbation of pediatric chronic pain; however, what about the role of biology? It is clear that an individual's genetic makeup contributes substantially to the experience of pain, with heritability estimates between 20-60% (Norbury et al., 2007), and animal studies showing a strong genetic propensity to develop chronic pain following nerve injury (Mogil et al., 1999). Clearly, the biological role in chronic pain is important to consider and many psychologists, myself included, underscore the importance of the biopsychosocial model (Gatchel et al., 2007) to conceptualize cases, explain human behavior and pathology, and formulate treatment plans. However, the processes through which the biological underpinnings interact with salient psychosocial variables to explain who is at risk for the development of pediatric chronic pain is not well understood. Examining the mechanisms that contribute to the transition from acute to chronic pain is necessary if we are going to propel the field forward and this will only be accomplished through translational research (Waldman & Terzic, 2008, 2010).

Translational research has two main purposes; to effectively translate new knowledge, mechanisms, and techniques generated in basic science laboratories into new approaches for prevention, diagnosis, and treatment of disease (Fontanarosa &

DeAngelis, 2002) and to translate the results from clinical studies into everyday clinical practice and health decision-making (Sung et al., 2003). Translational research is conceptualized in levels T0-T5. At one end, T0 includes basic science discovery and at the other, T5 includes the global health impact (Waldman & Terzic, 2010). Pediatric pain psychologists are in a unique position to contribute to these important research endeavors in translational research. Yet how do we go about doing this? Well, we on the 'bed' side of medicine (T1-T5) need to work at forging collaborations with the 'bench' side (T0) and vice versa, with the backward translation from T1 (first in human phase trials) and T2 (clinical efficacy) to T0 as well, the forward translation from T0 to T2 in order to impact care (T3-T5) which is what I did. I reached out to Dr. Michael Costigan, a distinguished neuro-biologist and pain geneticist at our hospital after he gave a presentation to our group. I was filled with trepidation when I entered the esteemed F.M. Kirby Neurobiology Center to meet with Dr. Costigan for the first time to discuss a potential collaboration. I had some research ideas of how we could collaborate but he is a world-renowned researcher who publishes in *Neuron*, *Nature Neuroscience*, and *Cell*. Would he really be all that interested in what a psychology fellow had to say? As it turned out, he was.

That meeting on May 17, 2011 was a pivotal moment in my career. It set the stage for a collaboration that has included preclinical and clinical models of chronic and persistent pain as well as presentations together at national and international conferences and collaborations around the globe. And we have both learned a lot from one another. Mike has shared that he now values the role of the environment on pain expression a lot more than before we met and in turn I have learned about how to set up and conduct animal models – never in a million years did I expect that I would be working with mice! We each bring a unique set of skills to this pain research marriage that allows us to ask questions and design studies that embody the biopsychosocial model. We are exploring the roles of biological sex, age, childhood stress, and genes on pain sensitivity with the hope that assaying the results of this environmental/genetic synergy will be to of great importance, especially in children where the risk of potentially lasting effects on neuronal plasticity is greatest. As a pediatric pain psychologist, the more I can understand the bench side of pain, the better equipped I will be at identifying patients at greatest risk and developing mechanistically based behavioral interventions for patients that are truly empirically based.

Some may ask – why mice? After all we have the perfect model, children themselves. The answer is that mice allow for us to control exactly the environment and the genome – both of which are crucial, as all diseases are the result of genetics and how the environment interacts with them. Being able to control the environment and the genome and selectively manipulate them is at the heart of scientific endeavor and we are able to conduct behavioral testing in mice that examines the key psychosocial variables of interest, such as anxiety (Open Field Activity) and social behavior (Social Interaction) (Crawley, 2004; Stanford, 2007). So even though rodents are not perfect models of patients, they are an essential piece of the translational landscape – one that should be constantly checked back to the patients and the issues that arise from their conditions. This collaboration, while amazing and transformative, has not always been easy. I have faced an uphill battle at times with some people questioning why I would pursue such research when I am not a trained lab scientist. I argue that my background in clinical psychology is an asset for the environmental and bed side component of this research. How do we truly move forward and integrate our research camps if such collaborations do not exist? Given that combining our unique skill sets is still novel, we have struggled with obtaining funding (but have recently been successful!) as well identifying publication outlets that are most appropriate for our work. Presenting our work to department chairs has been critical in conveying the importance of this work and gaining support for our continued collaborations. While our work is in the early stages, we know that our combined expertise and translational approach will only enhance our capability for developing individually tailored patient-oriented interventions (both at a behavioral

and drug therapy level; T3-T4) and delivering them to at risk youth.

I once read a Robert Holden quote that said: "One new perception, one fresh thought, one act of surrender, one change of heart, one leap of faith, can change your life forever." My career did change that day in May 2011 and I hope that my decision to reach out to a bench scientist will in turn be able to help the millions of children living with chronic pain.

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