Lessons Learned

In this issue, JAB continues a series of editorials from highly impactful faculty and researchers on “lessons learned” throughout their careers or lives. The hope is that the rest of us can benefit from their experiences. I would like to thank these individuals for sharing their thoughts with us.

—Michael Madigan, Editor-in-Chief

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In 2017, I was honored with the Muybridge medal from the International Society of Biomechanics (ISB). Recipients of this award are asked to give a presentation at the biennial ISB conference. My presentation was scheduled for Wednesday July 26, 2017, in Brisbane, Australia.

In preparation for the Muybridge lecture, I reflected on my career as a scientist. I had prepared my presentation months in advance. However, just prior to the ISB conference, I took advantage of the southern hemisphere winter and went cross-country skiing with a friend in New Zealand. While skiing in the Cardrona mountains and having lots of time to think, I started having doubts about my Muybridge presentation. Instead of summarizing all the research I had done, I wanted to talk about the scientific process, and what I had learned from that in my 40 years in science.

My revised talk was entitled *Reflections on Muscle: Intuition, Truth, Serendipity and Paradigms*. “Muscle” had to be in the title because it is the only thing that I can competently talk about, and “Intuition”, “Truth”, “Serendipity,” and “Paradigms” seemed to describe events and processes in my scientific life that formed me and taught me lessons that I thought might be useful for young and aspiring scientists. Allow me to convey 2 of those stories: they deal with “Intuition” and “Serendipity.”

Intuition

My PhD (co-)supervisor, Jim Andrews, a hard-core mechanical engineer and fabulous tennis player, had a saying: “go with your intuition, but never rely on it.” I interpreted this to mean that intuition was a good way to get started on a project, but at the end, you always need to check if your intuition indeed makes sense. I had my first strong intuition in science as a doctoral student when I started working in muscle mechanics. My goal was to solve the distribution problem in biomechanics, which required having some basic knowledge of the field. So, I started to read some of the classic works and came across A.V. Hill’s paper, “The Mechanics of Active Muscle,”¹ in which Hill makes the argument that muscles are unstable on the descending limb of the force–length relationship because of the negative stiffness of muscle at these lengths. Muscle segments and sarcomeres were said to tear each other apart: short-strong segments/sarcomeres pulling long-weak segments/sarcomeres beyond actin–myosin filament overlap, thereby overstretching sarcomeres, disabling their active force

capability, and leaving them damaged. This seemed a strange notion. The idea that muscles had evolved similarly in all species, with sarcomeres as their basic building blocks, and that these building blocks should be unstable and exhibit negative stiffness for approximately 60% of their working range, seemed preposterous. Was this an example of evolution gone wrong? Knowing little about muscles at that time and not having done a single experiment on muscles, my intuition told me that instability and negative stiffness theory was not a good idea, despite its support by the undisputed leader of 20th century muscle physiology. Not only A.V. Hill, but also other prominent muscle physiologists, including Andrew Huxley, supported the instability theory. He associated it with the “creep” phenomenon of muscles,² while others used it to justify the unexplained residual force enhancement and force depression properties of skeletal muscles (refer to the studies^{3–5}).

Approximately 20 years after my intuitive rejection of the instability theory, I was in a position to directly test if muscles and individual sarcomeres were indeed unstable; it turned out they were not. Pulling single myofibril preparations actively onto the descending limb of the force–length relationship did not result in the predicted negative stiffness, the catastrophic overstretching of sarcomeres beyond actin–myosin filament overlap (popping) did not occur, and the anticipated damage of sarcomeres and loss of force was not observed (refer to the studies⁶). Rather, sarcomeres stayed at constant (but different) sarcomere lengths (a phenomenon not fully understood to this day) and exhibited positive stiffness and perfect stability. Intuition, even in the absence of any knowledge of the specific field of research at the time, turned out to be correct.¹ I learned that intuition, more often than not, is an excellent starting point in science and has led to many exciting discoveries that, through mere logic, might not have been reached.

Serendipity

In my Muybridge lecture, I associated many of my contributions to science with serendipity. My favorite example is that of the discovery of the so-called “passive force enhancement” property in skeletal muscles.⁷ The aim of the experiments that led to the discovery of passive force enhancement was altogether different from what we found. The aim was to explore residual force enhancement properties of a muscle across its entire length and for all parts of the force–length relationship. While doing these experiments, I realized that passive force following active muscle stretching (and deactivation of the muscle) was much greater than when we performed passive muscle stretches to that same final length or performed purely isometric contractions at that final length. For some time during these experiments, I tried to figure out what we did wrong because I was convinced that somehow we had made a mistake: maybe we pulled the muscles to a longer length in active compared with passive stretch conditions, thereby producing this increase in passive force. But I soon realized that we had not made a mistake: the increase in passive force following active muscle stretching was indeed genuine. This discovery led directly to the premise that residual force enhancement was

associated with “the engagement of a passive structural element upon muscle stretching,” an idea that had been put forward before, but without experimental support.^{8–10} It also led directly to the notion that the structural protein titin might be a candidate for this passive force enhancement (refer to the studies^{11–18}), an idea that now has wide support, even though the molecular details of how this might occur remain largely unsolved.^{19,20}

A serendipitous observation led to a new field of investigation: the role of passive structural proteins in active force regulation in skeletal muscles. Attempts to publish this work were met with strong resistance and rightly so. It was an outrageous idea to propose that anything but actin and myosin were responsible for regulating active force. One final reviewer, after multiple rounds of revisions, insisted that this paper could not be published because “if this phenomenon (passive force enhancement) really existed, it would have been discovered before” as many people had been stretching active muscles for more than a century. And indeed, the reviewer was correct. Going back into previous literature, many scientists show passive force enhancement in their raw data traces, but none of them remarked on it. After all, passive force enhancement manifests itself after the muscle has been deactivated and the “real experiment” has been concluded. I was not the first to have made the observation. But I was the first to recognize it for its worth and its important implications for muscle contraction. I have made many completely unexpected observations in my scientific life, and it is often these observations that open the door to a new way of thinking, a new field of scientific investigation. Serendipity in science has led to many revolutionary discoveries, so be aware! Science rewards the prepared mind.

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Note

¹In fairness to all, it must be said that the notion of negative muscle stiffness, instability, and the development of large and rapid sarcomere length nonuniformities on the descending limb of the force–length relationship upon active muscle stretching continues to persist, despite ample evidence to the contrary.

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