Am J Clin Exp Urol 2018;6(2):32-36
www.ajceu.us /ISSN:2330-1910/AJCEU0075894

Editorial
Allowing awe in life

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Received March 12, 2018; Accepted March 19, 2018; Epub April 1, 2018; Published Apirl 15, 2018

This editorial and memorial article celebrates Donald S. Coffey, Ph.D., and reviews life-long lessons on science, life, medicine, mentorship, and our experiences in our analysis of cancer cell motility and metabolism.

The first time I met Donald S. Coffey was in late 1991 around midway through the first year of my medical oncology fellowship at Johns Hopkins. My classmates and I were attending a reception to meet prospective research mentors and to choose a lab for the ensuing 2 years, and Dr. Coffey was gracious enough to approach me to ask about my ideas and determine whether I may be a good fit to join his lab.

I told him I that I had spent two years after my internal medicine residency studying oncogenes in Harvey Herschman's lab at UCLA. While working with Harvey, I began to think a lot about what might be controlling cancer cells' abnormal shapes and movements, and I became obsessed with the idea that derangements of cellular calcium homeostasis somehow altered the way cancer cells respond to gravity and other forces. While scouring the literature, I came across several papers showing that electromagnetic fields can lead to the release of calcium ions from cells and can promote cancer. I told Dr. Coffey, who everyone affectionately called "The Chief", that I wanted to pursue these ideas during the next two years. I fully expected him to smile politely and walk away after hearing my unconventional ideas, but I quickly realized that The Chief was not interested in conventional ideas. He seemed to like the fact that I was thinking outside the box. Rather than walk away, he extended his hand to offer me a position in his lab, and I enthusiastically shook it.

One of the greatest things about The Chief, among many great things, was the fact that he allowed us complete freedom to pursue any idea, no matter how outlandish, as long as it was testable. Chief had heard about a device that could cyclically stretch cells growing in culture, so he suggested I determine whether growing prostate cancer cells in the device would change the expression of certain cytoskeletal proteins we were studying. After many attempts, I found that stretching cells had absolutely no effect on expression of the genes of interest in a variety of rat prostate cancer cell lines. Like everyone else at the time, I used GAPDH (glyceraldehyde-3-phosphate dehydrogenase), the glycolytic enzyme, as an internal loading control for those RNA expression experiments. Annoyingly, I found that GAPDH expression varied wildly between the different cell lines and was therefore worthless as a loading control. Worse yet, my dream of having something meaningful to submit as an abstract in time for the next AACR meeting was shattered. Resigned to discarding the results and quickly moving on to another experiment, I nonetheless showed the northern blots to The Chief. Surprisingly, he was not the least bit perturbed, but instead became pensive as he silently contemplated the age-old question that he often posed: *"If this is true, what does it imply"?*

He immediately directed me to meet with Bill Nelson, who had just finished his oncology fellowship at Hopkins and who had worked at the very same lab bench that I had just inherited. I like to tell people that Bill Nelson is one of the smartest people I have ever known. However, unlike many smart people, Bill is also incredibly gracious and generous with his ideas and friendship, which may partially explain why

he now serves as Director of the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins. At that time, Bill was a newly minted Assistant Professor. As soon as he saw the northern blots with GAPDH varying wildly in the cancer cell lines, he asked me if I had ever heard of Warburg. I thought Warburg was some sort of fancy cheese, so he recommended I become familiar with Otto Warburg's observation that tumors display increased levels of aerobic glycolysis as compared to normal tissues, an observation for which he won the Nobel Prize in 1931.

Through conversations and data analysis with Bill Nelson, Alan Partin, the Isaacs brothers, The Chief, and others over the next several days, we observed a remarkably high correlation between GAPDH RNA levels from my northern blots and the metastatic potential and motility of prostate cancer cell lines, as had already been measured by Partin and others using video microscopy. I had no idea what to make of this observation, so The Chief went into action mode: he pulled an all-nighter and furiously read all manner of biochemistry texts and research papers in order to generate a plausible interpretation of the data, which he illustrated for me in technicolor flow diagrams on several pages of yellow legal paper the next morning. He then suggested I submit that story as what he called a "promissory note" abstract for the upcoming AACR meeting in time for the deadline later that day. I did so, and over the next few weeks I wrote and submitted a manuscript to *Cancer Research* that described our observations and put forth our hypothesis that glucose consumption via the glycolytic cascade was fueling cancer metastasis [1]. Experiments years later from my own lab in Houston argued against this hypothesis [2]. Nonetheless, *Cancer Research* accepted our paper without revision within a few days. Seeing the acceptance letter fresh off the fax machine, Alan Partin declared that he had never heard of a paper being accepted without revision, which is saying a lot considering how many papers he had already published by then. That experience taught me important life lessons that The Chief often expressed and later published in a perspectives paper [3]: 1. The experiment that didn't come out the way you thought it would is the only experiment that is really going to teach you something new. 2. Every datum is screaming to tell you something, but you must do the listening and thinking.

The Chief also demonstrated the value of hard work when he spent all night reading and thinking in order to help me develop an abstract for the AACR meeting. I remember he once told me of a time when he was still a graduate student at Hopkins and stopped to chat with the security guard on his way out the door one evening. The young Don Coffey wondered aloud what it would take to succeed in science. Thinking that he had posed a rhetorical question, he nonetheless received an answer from the security guard, who had never spent a day in a research lab. The guard gestured to a window in the building across the street, and said "I don't know who works in that lab or what he studies, but I know he will succeed". Surprised to receive an answer, Don Coffey asked the guard how he could possibly make such a prediction. "All I know is that the lights in that lab burn bright every day until the wee hours of the morning", he replied. Working with The Chief gave me a newfound appreciation for hard work, perseverance, and the character traits that he attributed to "scrappy street fighters", a moniker I strove to earn.

The Chief was not all about science. Many people can undoubtedly recall countless stories about tea ceremonies on the Brady lab veranda, lab picnics, softball games, dinners at Fells point, flaming bill folds, booming civil war cannons, and other festivities. However, the outing that stands out in my mind more than any occurred on March 21, 1994, which was a snowy Monday. It must have been a holiday, since The Chief decided to rent a large van to lead a lab excursion to Washington DC to take in all the sights and regale us with US and Civil War history. My wife Linda was 39 weeks pregnant with our first daughter, Margeaux, so she was concerned about walking around in the snow all day. Nonetheless, The Chief convinced her to come along, so Linda gamely traipsed around D.C. until late that evening, with her overcoat unbuttoned to accommodate Margeaux. The trip went just fine from the obstetrical standpoint, but Linda noticed her fingers swelling dramatically as the day wore on. The next day, with her obstetrician Emily Haller's blessing, I flew to New York to interview for a faculty position at Memorial Sloan Kettering. When I arrived at the Hospital for my

interviews, I immediately called home to check on Linda, who I soon learned was in Labor and Delivery at Hopkins Hospital. Needless to say, I skipped the interviews and returned to Baltimore in time for the delivery later that day, March 22. As Linda was in the process of pushing Margeaux out, we heard The Chief's booming voice, with his Bristol Tennessee accent, from outside the delivery room: "Is this a good time to visit"? Between breaths, Linda politely asked "Can you give us a few minutes, Dr. Coffey"?

After serendipitously discovering that GAPDH expression correlated with cancer cell motility and metastasis, my focus turned to what The Chief liked to call "old time religion", namely energy metabolism in cancer cells, a topic that was sexy in the 1920's but became passé as soon as Paul Berg cloned a gene in the late 1970s. It turns out that there has been quite a resurgence of interest in glycolysis in tumors in recent years, but I was quite the Don Quixote for much of my scientific career. I continued studying nutrient metabolism in cancer cells when I took my first faculty position at Baylor College of Medicine in 1994. A few years after joining the faculty at Baylor, I became fascinated by studies that showed that cancer cells are even more dependent upon the essential amino acid methionine than normal cells are [4]. I then shifted my research focus from GAPDH and glycolysis to methionine [5-8]. In addition to lab studies, we even published results of a phase I trial of dietary methionine restriction in patients with refractory cancers [9]. The methionine topic fascinated The Chief, since he immediately saw the many critical roles that methionine plays in cancer cells, from methylation, to folate metabolism, to polyamine synthesis. I only wish I had The Chief around full time when I ran my own lab, not only for his scientific insight but also for his boundless enthusiasm.

Naturally, as I worked in the lab, I also cared for many patients with advanced cancer and supervised medical students, residents, and oncology fellows. As I did, I distinctly recall a day when I had an epiphany about the doctor-patient relationship. I was rounding with an oncology fellow on the consult service, and we faced the unenviable but all too common task of telling a man that his colon cancer had recurred and was now metastatic. As I observed the oncology fellow discuss results of the man's CT scan that showed liver metastases, for some reason I was struck by the fact that he spent nearly the entire time speaking in technical medical jargon while never exploring the patient's perspective. While the conversation was typical of many such conversations, I could nonetheless sense that something was terribly wrong, even though I could not exactly put my finger on it at the time. In retrospect, I realize that The Chief would never have handled such a delicate conversation in that way. He was a master at explaining complex ideas in the most understandable ways to anyone, and he was deeply empathic. After observing the fellow, I became as fascinated by the psychosocial aspects of oncology as I am by basic biomedical research.

Over the next few years, I intentionally phased out my lab and studied the medical communication literature as voraciously as I had studied the cancer research literature. I began to consider what practices, attitudes, beliefs, and skills doctors need to connect with vulnerable patients and families who face grave illness. I arrived at a fuller appreciation of the distinction between healing illness and curing disease and learned that navigating heart-wrenching and difficult conversations with patients and their families takes tremendous skill and knowledge that can be taught and learned. I transitioned from medical oncology to palliative medicine nearly six years ago. My time with The Chief through the years undoubtedly influenced me profoundly during my career evolution. As creative and brilliant a scientist as Chief was, he was even a more brilliant student of human nature who forged deep and authentic bonds with everyone who entered his sphere and by extension countless others throughout the world. The Chief treated everyone around him the same way that great doctors treat their patients, namely with love and compassion. When I get in a bind, I still often ask myself "How would Chief handle this situation"?

While I am still fascinated by exciting discoveries in cancer research and treatment, I now spend all of my clinical time tending to the symptomatic and psychosocial needs of patients with advanced cancer and their families. I focus on teaching oncologists, palliative doctors, and many others the skills they need to succeed in the hardest conversations [10-15],

and I use storytelling to help teach those skills [16-20]. In many ways, I have come full circle. The last time I saw The Chief was in March 2017 when I traveled to Baltimore with Linda to visit our younger daughter, Eden, who is now a senior premed student and member of the women's lacrosse team at Johns Hopkins University. During that visit and others, The Chief expressed as much pride in my accomplishments as a healer, my passion for humanism, and my love of my family as in my research accomplishments.

A few nights ago I was facilitating the Healer's Art, an elective to foster humanism, self-care, and reflection for medical students at Baylor College of Medicine and The University of Texas at Houston Medical School, including my daughter Margeaux, who is in her first year. Our session that evening was devoted to "Beyond Analysis: Allowing Awe in Medicine". As the students and I were settling in for our small group session, I overheard them bemoan the fact that they have to memorize vast quantities of seemingly irrelevant information during medical school, as medical students have done for over 100 years. Yet, I thought about how awesome the human body and all of its parts are. Each amino acid has its own personality: one bends peptides, another becomes phosphorylated, and yet another receives methyl groups, all part of an intricate and elegant ballet. Every muscle, neuron, receptor, and ligand is highly adapted to coordinate seamlessly with the rest of the body. The extracellular matrix, cytoskeleton, and nuclear matrix all resonate as one [21]. As the students spoke, I felt compelled to offer my perspective, to help them see why their onerous learning is important and always will be. I found myself sharing some wisdom from The Chief: *"You are going to be surprised at the simplicity of the real answer. Almost a billion years went into selecting the system that you are studying. Remember, Crick and Watson didn't make the double helix, they only discovered an ancient system still operating today* [3]*".* And so, The Chief's legacy lives on in the next generation of young healers, and forever.

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