Answering a Call to Action

By Krystle Frazier, MD

Much of my undergraduate career was spent whimsically learning any discipline available from primate ecology to linguistics to race and ethnicity. My college transcript depicts a wonderfully *liberal* and *artsy* college experience. To the undeniable surprise of some of my peers, my very non-traditional approach to education still led me to a career in medicine. What then, could spark enough fire to convince this self-proclaimed "type B person" and Comparative Human Development major to focus her intellectual curiosities upon a career in medicine?

I do not remember the exact chronology of happenstance moments where I fell upon the right information to impassion me to commit to a medical career in Pediatric Hematology-Oncology. My journey has been untraditional and full of twists, turns, disappointments and what I can only call divine interventions. Nonetheless, I will start with the information that shook my core the most.

In 1972, studies were published justifying the "increased use of surgical sterilization and therapeutic abortion" as the gold standard of prenatal advice for women of reproductive age living with sickle cell disease (SCD), specifically genotypes *HbSC* and *HbSS*.[1] In 1989, my mother, who has sickle C hemoglobin disease (HbSC), was advised to terminate her second pregnancy. She decided against that recommendation, and in 1990, she had a cesarean delivery of a full-term baby girl and celebrated my birthday. Many years later, in 2001, a retrospective cohort study done by physicians at Grady Memorial Hospital showed that simple improvements in the management and quality of care for patients with SCD lowered the perinatal and maternal mortality rate for deliveries occurring between 1980 and 1999.[2] Such research provided women living with SCD the full spectrum of options in childbirth that "healthy" women enjoy without question.

The history of SCD, its discovery, management, and intersection with healthcare disparities in the United States is endlessly intriguing, yet often infuriating, to me. SCD was the **first** "molecular disease" to be documented in humans. This means that it was the first disease for which we knew that a particular set of symptoms in humans[3] was caused by a change in protein morphology[4] (polymerization of hemoglobin) due to the replacement of one amino acid[5-7] (glutamic acid to valine in the 6th codon of the β -globin gene), in the replicating DNA of a protein (β -globin), as the result of a single nucleic acid substitution[8] (adenine to thymine). Yet, for decades, this historical disease had only one major therapeutic treatment option: hydroxyurea, which does not actually target the pathophysiology of the disease and has questionable efficacy. In addition, hydroxyurea cannot feasibly be globally utilized to treat patients in countries bearing the most significant burden of SCD

I realized that my biology classes from high school and medical school focused on the findings of SCD research conducted in the late 1940s to late 1970s. I made it my personal mission to learn more and found that the current body of research has grown tremendously since the first "sickled cells" were observed by James B. Herrick in 1910. We now know that the symptoms that manifest in SCD are not the result of those sickled cells alone. Endothelial cells,

inflammatory cells, and various other cellular and soluble molecules, unaffected by the β-globin mutation, have been purported to be involved in the pathophysiology of SCD.[9,10]

During the pivotal year I took off from medical school to pursue basic science research, I was fortunate to meet a principal investigator who is also suspicious that derangements in the activity of these other cells play a key role in the symptoms that result from that one little nucleic acid substitution. His work implicates a hyper-inflammatory state in the pathophysiology of acute chest syndrome, one of the leading causes of mortality in SCD. He has shown that patients with SCD have elevations of cyclo-oxygenase (COX) pathway mediators (prostaglandins and leukotrienes) in their urine and blood serum even when in their "healthy state" at routine clinic visits.[11,12] His work connects to prior research demonstrating a peak in secretory phospholipase A2 (sPA2), a key inflammatory mediator of the COX pathway, as a possible predictor of the onset of acute chest syndrome.[13,14]

My work with this PI inspired me to dually focus on my desires to provide clinical treatment to patients with SCD and pursue my dedication to scientific inquiry. This investment in the integration of molecular research to the clinical outcomes of patients resulted in the development of the first FDA-approved medication targeting the known pathophysiology of SCD at the same institution where I began my journey working in the area of SCD. I celebrate the growing body of research that has provided more options and more equitable care to patients living with sickle cell disease. As I celebrate, I also accept the challenge in my own budding career of determining the role I choose to play in addressing health disparities in minority populations who are affected by SCD. My hope is to continue the scientific discourse in this area to give rise to more research in this field.

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