Reflections

On particles, policemen, and punctuation: Reflections on scientific writing

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Almost 80-years-old, I still work full time and occupy the same small office in the Durham Veterans Administration Medical Center that I acquired in 1980 when I began my independent lab career. The office is cramped, the walls a faded yellow, and my desk is strewn with Xeroxed copies of journal articles. While the office is meager, it has been the site of joyful productivity. Discovery has been my goal, not a corner office so I could gaze at the gothic splendor of Duke Chapel.

I have always aspired to be a triple threat—researcher, clinician and teacher. Times have changed, however, and the likelihood for a trifecta has just about vanished. I still teach and see patients, but my true passion is the lab. I have a small operation, a boutique lab so to speak. My science is good, but I cannot compete with large groups who have big armies to generate big data.

Not too long ago, I embarked on a new line of research that I thought was really nifty. Unfortunately, the experiments were more difficult than I anticipated, and technical challenges mounted. My anxiety increased along with the inevitable concerns about my career and whether I should forge on or close up shop. I fretted about a comment in the critique of a grant submission: "The work is descriptive and represents a limited extension over prior studies. Innovation is lacking." Perhaps this was code for Enough already, it's time to stop.

Given the force of these worries, I felt pressed to quickly revise and resubmit a paper that had been recently rejected. Even though my office is dreary, I decided to work there instead of at home since my wife was hosting her bridge group. My wife's friends (The Bridge Nuts) are wonderful people, but after a few glasses of Yellow Tail chardonnay, the laughter gets loud, my nerves fray, and I get discombobulated.

I tell my trainees that science is about reading and writing, and that they should focus as much attention on the quality of the writing as the design of experiments. Even with a rejected paper, I always want to see the comment that the paper was well written.

As the senior author of the rejected manuscript, I took a stab at some revisions, trying to upgrade the version written by the fellow even though it was quite good. I hoped I could sharpen the paper's focus, make the discussion more engaging, and give the story more zing.

The discussion in the revision started with the following sentence: "These studies provide important new insights into the mechanisms of inflammation." The sentence was a standard opening for a discussion. I knew it was unoriginal and I dithered whether to retain the word "important."

Like Oscar Wilde who put a comma in the morning only to take it out in the afternoon, I had done the same with "important." I had put it in and then taken it out only to put it in again.

Important was a big retreat from "striking" which had been in the first version of the paper sent to a journal

with an impact factor in the double digits. Without review, the journal rejected it in just 24 hours, the response coming back with wounding and blistering speed. Once my ego recovered, and we completed the revisions, we planned to submit the paper to a journal whose impact factor was less lofty.

With an impact factor in the middle of the pack, "important" may be about as good as it gets for insights, but the acceptance of the paper was key for a grant which I intended to submit for the next deadline.

On the day that I worked on the revision, Durham had been remorselessly hot. The temperature was more than 90 degrees, the heat and humidity dense. At 6 p.m. in the evening as I drove on the interstate to the hospital, blue-black clouds darkened the sky, thunder rattled and leaves flew in the swirling wind. Then, driving rain pummeled the city.

Having forgotten my umbrella, I ran from the parking deck to the hospital entrance, and when I got to my office my shoes and clothes were soaked.

Once in the office, I dried myself off with paper towels and started to once again attack the opening sentence of the discussion. That sentence fluctuated in size and tenor as my mood zigged and zagged. I restudied the sentence. The words looked clean and solid in Arial 11 font but the language was dull and tired and devoid of any of the excitement I felt when we began.

When the study described in the paper had its start, I felt jazzed and blessed with good luck: blood samples from volunteers given lipopolysaccharide or bacterial endotoxin (LPS) and a post-doctoral fellow who was a whiz with a flow cytometer. The volunteer study had been performed many years before for another reason but the samples remained. A few hundred microliters of plasma from each subject had been stored safely in a box in the -80 degree freezer. Even though the box was crusted with ice, the samples were in good condition, the labels intact and, readable.

I like to do experiments on LPS as it is a key mediator of sepsis. Like many scientists competing for grants, I have to be realist and follow Sutton's law, which is named after bank robber Willie Sutton who, when asked why he robbed banks, answered, "That's where the money is."

Sepsis is a terrible problem that has defied the development of new therapy. Far more people succumb from sepsis than rheumatoid arthritis and systemic lupus erythematosus, the usual areas of my research. It can be easier to frame a paper or grant about sepsis and start with sentences like, "Sepsis is a major cause of morbidity and mortality and accounts for 100,000 deaths per year. This syndrome results from profound immune system changes mediated by LPS."

The paper I was revising concerned microparticles. Microparticles are small vesicles released by immune cells stimulated with LPS or other agonists of toll-like receptors. Originally thought to be debris, microparticles are now conceptualized as vehicles for intercellular communication because of their cargo of immunoactive molecules. Much smaller than ordinary cells, microparticles are abundant in the blood and have powerful actions that can mediate inflammation and promote thrombosis in many conditions including sepsis. From our previous work in cell culture systems, we had predicted that macrophages would be the key producers of the microparticles that populate the blood.

The study was straightforward: measure microparticles in the blood of the volunteers given safe doses of LPS, barely enough to notice. Using markers for different cell populations, the post-doctoral fellow assessed whether, with LPS administration, the number of particles in the blood increased.

The experiment worked beautifully. By flow cytometry, total particle numbers rocketed up, but my heart sank as the fellow and I carefully inspected the data. The macrophage plot showed a faint smudge, but the platelet plot was black and dense with dots. These findings meant that the particles were coming primarily from platelets and not macrophages as we anticipated.

There is nothing wrong with platelets, but I don't know anything about them and lacked the background to frame the story. I know macrophages. For me, platelets are a wilderness and terra incognita. How could I discuss cells that lack a proper nucleus and seem like ghosts? Even if I could decide whether the insights were important, I would be clueless to say why. I scoured articles in journals like *Thrombosis Research* and *Journal of Thrombosis and Hemostasis* but I was clearly adrift and the text of the discussion was tentative and replete with uncertainty.

As I fiddled with the first sentence in the discussion, I heard a knock on the door. The knock was angry and insistent. "Who's in there? This is the police," a deep voice rumbled.

Immediately, I panicked. What had I done? Maybe I was violating a rule by working after hours. I knew that I was behind on my CITI training, failing to do modules on hazardous waste disposal and government ethics, but I could not imagine my tardiness merited arrest on federal charges.

Perhaps, it was a raid on my computer to make sure I was not logging into anything salacious. I was concerned that I was on a watch list since, a few months previously, I had set off an alert on the clinic computer by Googling "Brides from the Philippines." As I explained to the IT security person—a stern woman with cold eyes—I was only demonstrating to one of our fellows the way some veteran patients can search for companionship. We had just seen an older man with painful arthritis. As the patient related to us, he lived by himself in a trailer near the coast and was lonely. He wondered what he could do, but I remained silent.

I swiveled around in my chair, stood up and opened the door with trepidation. There I confronted a large man with a dour face in a deep blue police uniform. The policeman towered over me. He had a flak jacket with a whole arsenal of weaponry. On his belt was a night stick that looked as big as a baseball bat, and had an ominous black sheen.

"What are you doing here?" he growled.

"Working, sir," I said meekly and showed him my ID badge which has a picture of me looking old and grim. The photographer told me not to smile. Apparently smiles make it hard for computer security systems to recognize a face.

"Ok, just checking," he said, adding, "make sure you lock your computer and sign out."

Even though the encounter was routine, I felt rattled and unnerved, the cop treating me like a teenager wandering in downtown Durham.

Feeling thirsty, I went for a drink of water. I work in the research wing of the hospital, but use the fountain near the main patient waiting area. As I sipped the slightly warm water, I imagined what was happening upstairs on the medicine service where I had attended for more than 40 years, stopping only with COVID when age put me at risk.

I knew the type of patients who would be hospitalized on the wards: A 30-year-old man with raging cancer retching up the Bojangles fried chicken bought by his stricken mother; a Korean War veteran, thin with wispy white hair, staring blankly as life fades away; and a Viet Nam veteran with diabetes, septic and bacteremic, the famous army of the white cells marching off to do battle, although I suspected that Pseudomonas would soon win.

As I walked back to my lab, I pondered for a moment whether I could get any blood from the man with sepsis and look for microparticles from platelets. Even if it was one person, I could describe the findings in the paper, putting preliminary results in parentheses. The data would be a nice addition to the volunteer study, boosting the relevance, maybe catching the editor's eye. Immediately, I discarded the idea. My IRB protocol covered lupus not sepsis. More likely than not, the platelet particles would have already disappeared and then what could I say?

It was 10:30 p.m. The bridge group would be gone, and my wife would be filling the dishwasher with wine glasses and plates covered with ice cream and crumbs of the apple tart she baked.

I closed my eyes to refresh myself for one final go on the revision. I reflected on how I have scrambled between the bench and bedside for almost 50 years, and still confront the usual challenges that seem never-ending: precarious funding, an onslaught of obligations, and too little time for too much work.

I am singed but not burned out. I still savor the work, although as Thomas Mann said, a writer is someone for whom writing is more difficult than it is for other people. That is certainly the case for me.

Putting the finishing touches on the paper, I corrected a typo and reconfigured a long sentence, eliminating an "and," replacing it with a semicolon. I was pleased by the evening's work and saved the document to the hard drive as a version called "final."

I read the first sentence again, and my spirits lifted. I was proud of my resolve since I restored the first sentence of the original version. Even if the paper had been rejected once, I would go with a strong statement. I was convinced that, if platelets emit particles after a jolt of LPS, the insights for inflammation are more than just important, they are downright striking.

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