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1: The Turn, away from the traditional system

A first-hand, inside-out account of how the traditional system changed over the last 15 years and how it affected a scientist and his science.

I was reduced to routines. I had to get out of bed at daybreak and get to the lab by 8 AM, even though there was nothing to do there. I would slip in and out of the office or laboratory, avoiding conversation or eye contact, just as I had observed other scientists without grants doing. The challenge was not any more this experiment or that technique but the hands on the clocks that seemed to be stuck. I had wondered what scientists without grants do, and now I was finding out. Apparently anything that represses their second nature of devising experiments and interpreting results. Even the regular scanning of the table of contents of scientific journals had ceased because many scientists whose papers I found interesting were silent or had changed course. The new routine was 'being busy' doing futile things in the lab or seeking Internet escapes for the mind.

Until it happened, about two years ago, maybe on a day when the gloom-doom saying that was scoring the most wins in my mind was Paul Newman's second law: "Just when things look darkest, they go black." I was grasping hope one moment and loathing it the next, when I clicked on the YouTube video *The truth [is, what is]*. As I watched it over and over again, I must have entered an anti-Twilight Zone, with Lenny Bruce in place of Rod Serling. By the time I got into my '94 Camry (which had become my cocoon) to head home that evening I had begun to turn. 'What is' became my knife for cutting the crap out of my mind. Soon it became clear to me that what was bothering me most was not losing my ability to continue research as I had assumed. It was a deep-seated fear of dependency, which in my situation meant fear of life itself. It was indeed my existential problem at that time, because once I found the solution to it, I calmly started to think about what to do with the rest of my life. I focused on the question of 'how could I use my experience as a scientist to enable all interested scientists to conduct research and produce the best possible data on any subject matter, without being inhibited by funding constraints and the problem-ridden grant application, review, and award processes.'

I found the answer by pursuing two very personalized questions: 'why am I *not* doing what I *was* doing,' and 'how could I have kept on doing it?'

Let me explain. I secured my first big research grant (an R01 from the National Institutes of Health) the very first time I tried, as a post-doctoral fellow. The data in that grant application pointed in a new direction for research in my area, one that raised more questions than it provided answers. Nonetheless, the reviewers liked it, and I was ecstatic. The year was 2001, when 25-30% of the grants were funded. I started my own laboratory hoping to spend the rest of my life doing what I love most, researching a topic in developmental genetics that intrigued and fascinated me.

The new data I obtained with that grant raised even more interesting questions, some of which were contrary to the conventional model and pointed in unexpected directions. This turned out to be a bad thing in 2005-2007, when I attempted to renew my grant or secure another one. The ground had markedly shifted, with only about 10-15% of grants being funded. At this time, the reviewers expected hypotheses that were solidly supported and experiments that yielded clearly predicted and explainable results. Although I cried foul then, it is not surprising to me now that my grant was not renewed and none of my other applications at that time garnered funds. You see, I was off on a path exploring a basic cell differentiation mechanism from an evolutionary perspective. Often I had to complete an experiment just to know what the next experiment ought to be, let alone form a robust hypothesis in advance.

Since tenure applications by scientists without an on-going or imminent research grant are generally rejected, I faced the grim prospect that usually confronts such scientists: giving up career as an independent researcher, taking up an unsatisfactory job, and moving at a very inopportune time for the family. I just could not bring myself to abandon my research aspirations or disturb my family. So, I took the opportunity offered me to get off the tenure track and onto the non-tenure research track. Being a bench scientist I was able to continue research, publish papers, and submit grant applications. I often had to use personal money for laboratory expenses, and sometimes earned limited salary through substitute teaching or bartering my bench skills. By about 2009, after being on my research path for more than 17 years, I had convincing clues for identifying an important evolutionary developmental mechanism, one involving mother-offspring interaction at the molecular level. Running out of options, and with great trepidation, I used the clues in an application for an NIH Exploratory Two-year Grant Award (R21). The high risk paid off and I got the grant in 2010.

Sure enough, and once again, unexpected results intervened and I ran out of money, just when I was approaching the most interesting point in my research and facing a challenging set of experiments that required time, trial-and-error approaches, and expensive reagents. From 2010 to 2013 I did what most scientists do all the time: write one grant application after another, almost every funding cycle, to both federal and private agencies. None were funded. Disconcertingly, the reviewers' comments now often referred to my non-tenure track status, revealing added difficulties scientists with non-traditional positions face in obtaining funds for their research. Since I was working with little or no salary from about November of 2012, I was running out of personal savings too.

From 2006 onwards, I became increasingly frustrated and bitter. I was failing despite taking every piece of reasonable advice that I got (from both successful and struggling scientists), doing my best to act on it, and publishing. I could not publish too many papers or publish them in high-profile journals because I had neither money nor time to obtain the irrefutable data required for those journals. I found validation, often repeatedly, to many of the other reasons my colleagues thought their grants were not funded. I joined the chorus, blaming every aspect of my research at one time or another: grant reviewers, study sections, model organisms, translation research, my institutions, funding agencies, politicians (for not increasing funding to federal agencies), publishers, not being tenured, my own data for not fitting the conventional model, my own inability to develop a convincing hypothesis with the data on hand, etc. The list can go on.

With each rejection, I found a new bottom and one more nightmare became a reality, or a wish. Without even realizing it I had entered Beckett's world (imagine *Waiting for Godot* inside *Unnamable* urged on by "You must go on. I can't go on. I'll go on"), driven by the delusion that this new paper or new data would please reviewers and get me a grant. Besides, I did not know what else to do because I could not bring myself to do something that did not interest me just for the sake of earning a living.

I do not know whether the Lenny Bruce video that I watched in mid-2013 helped me realize that I might never get funded again or merely accept that possibility. In any case, very soon after that I was examining myself as an experimental result. I concluded that I was a failure, not a loser. The problem was not in me, or in my colleagues and peers suffering a similar fate, or even in any of the other aspects I had blamed in the past. *The problem was the system itself and I, as well the large number of colleagues suffering a similar fate, was a byproduct of its dysfunction*.

When articles started appearing in 2014 — written by prominent scientists, research administrators, journalists, and politicians, both in prominent scientific journals and general newspapers — sounding alarm about the problems affecting scientific research, I did not feel the pathos of a victim. Instead, I felt satisfaction, the kind I experience when new experimental data support an earlier interpretation. And I felt dissatisfaction at the fixes proposed by authors in these articles. I found some of them reasonable, but realized that they would have minimal impact. I found others to be unworkable, unrealistic, or unsound. Furthermore, some of the problems that I felt were important were not addressed.

Chief among the unaddressed problems has been the dissipation of romance and adventure from scientific research. I trace my initial spark of interest in research to one hot summer day in my father's library a long, long time ago when I reached out and pulled a book to read, which happened to include a biography of Faraday. It made a disinterested and underachieving average student think that he could be a scientist! I feel sad for today's students for whom the love for research is mostly unrequited. Due to the enormous emphasis placed on science in K-12 education, and surrounded by boundless evidence of the impact of science on society, many students approach higher education wishing for a career in research. They quickly learn the incredible odds facing them and fear struggling like their professors or graduate student mentors. Most end up pursuing other careers, ones that provide a reasonable chance for a sustainable livelihood, if not wealth and fame.

I also think that marginalization of bench scientists is a serious problem. I find it incredible that today a scientist conducting experiments at the bench is not only a rarity but also generally considered to be a failure or lacking eminence. I believe that scientists who continue to work at the bench possess one of the best traits for research: they are attached to the process, which benefits from their passion, rather than to (often misleading) results and outcomes. In addition, these scientists will have first-hand knowledge of all aspects of experimentation and all the results obtained (both those that fit a model and those that do not). The confidence that comes with such knowledge is, I believe, the key to a healthy irreverence and skepticism that are important for progress. If I did not see others' data in my results and did not know what data are excluded in others' papers, I would not have pursued my research path despite rejection upon rejection and at considerable personal cost.

My experience with the traditional research system might be unique at the personal level, but it is definitely not at the scientific level. I know personally very many scientists who are also frustrated, and stymied by their experience. To get a feel for the scale of the problem, consider these

figures: in the last decade, about 375,000 out of about 450,000 applications have been rejected by the National Institutes of Health and out of about 75,000 that were funded, 50,000 were not renewed (Grant success & renewal rates). The precise numbers of people laid off from research and prevented from even starting a research career as a consequence is unknown, probably unknowable. Indirect inferences indicate that the loss is substantial. In one report, about 45% of the scientists indicated that they have either laid off or considering laying off research personnel in their laboratories and about 54% of scientists reported that they know a colleague who has lost a job (Budget cuts & scientists layoff). Thus, it is apparent that there are *tens of thousands of scientists in the U.S. who are regularly losing funding and thereby their ability to conduct research*, or are forced out of independent research careers because they failed to secure funding after spending about a decade getting trained for the job.

The unfortunate consequence is that the talents and resources of a large number of very knowledgeable and highly skilled people are being wasted. They could be making valuable contributions to science and society but are prevented by the way the current system works. Basic research scientists are more severely affected despite the historical proof that good and free-ranging basic science research leads to breakthroughs in applied science. Look at what Scientific American magazine has to say on the current status of research in the US: "Whatever model or models the nation chooses, many observers believe that the existing system of research by professors who constantly produce large numbers of scientists unlikely to achieve their career aspirations is near collapse. The real crisis in American science education is not young Americans' inability to learn, or the schools' inability to teach, but a distorted job market's inability to provide them careers worthy of their abilities."

To me the critical part of the above quote is "...inability to provide them careers worthy of their abilities." This inability is not merely due to funding level problems but also due to significant mechanism (for selecting grants for funding) and data problems that are also undermining science today. Too much emphasis has been placed on funding level as if science would become better if only funding were increased. The fact of the matter is that if funding was increased without addressing other problems, data in aggregate, and thereby science in general, would become worse. Also lost in the clamor for more money is the fact that in the current socio-economic-political climate the most we can expect is a small percentage increase in funding. Thus, we would have a few more scientists conducting research but the system would continue to be inefficient by wasting resources, perpetuating underachievement, squandering opportunities, and producing weak data.

That was unacceptable. So, I challenged myself to develop a fix that simultaneously addressed all the funding, mechanism, and data problems with the money that is already available for research. In all my thought experiments, my primary guides were scientists who continued to work at the bench even after becoming established principal investigators. These scientists are personally involved at all levels of research, from the generation of primary data to securing funding. Any fix that pleases them at all levels of the research process ought to address all fixable problems in the current system. I failed to find a viable fix for the current system that did not require additional funds or showed potential for producing significant changes without worsening or adding negative effects. However, in the process I realized that I could create a new, limitless system for scientific research that addresses all problems in a comprehensive manner while enabling scientists, in particular bench scientists and small laboratories, to not only self-sustain their research careers on their own terms, but also produce superior data most efficiently. That realization, and how it would help so many scientists pushed out of a research career for the wrong reasons, provided the purpose for the remainder of my life!

I stopped writing grant applications (the last one was in November 2013). I did bench work just to complete projects that could be published with the resources I had and kept alive only one project (mother-offspring interaction in embryogenesis) hoping to somehow take it to the publication stage someday. I started making early withdrawals from my retirement funds to support myself, meet my family obligations, and initiate work towards creating a new system for research. I figured that my retirement fund would last between 4-5 years, which is a reasonable amount of gestation time for this effort. So far I have developed a concept for the system, filed a patent application for it, incorporated a non-profit company in Delaware for development and operation in the U.S. (Assured Science Exchange, Inc.), assigned the patent application to this company, and launched this website for the purpose of recruiting founding members and kindred spirits to the effort.

I am aware that the traditional scientific research system in place today is more than 400 years old and has evolved over the years to serve the enterprise reasonably well. But the problems that have developed over the last 10-15 years indicate that it is not well suited to handle today's scope, volume, and complexity of the scientific research enterprise. Something needs to be done before a large number of competent scientists are run out of business and future scientists are scared away. If this effort seems quixotic to you, you are on track but missing the point. The adventures of Don Quixote are but instruments used to make the point about values in a system. If this effort ultimately leads to achieving even a tiny fraction of the

impact that book had on world literature, then scientists, scientific data, and the general public will all benefit immensely.

The concept for the new system is a basic framework, developed to the best of my abilities. I am sure that this concept or something vastly better will evolve once more people with different and superior expertise get involved. Even the prototype I have now has the potential to increase the number of funded scientists ~3 times, generate ~3 times more money for institutions, and produce vastly superior data, all at one-third of today's cost. Consider this combination of benefits in the light of today's socio-political and scientific climate and imagine that it can get even better! Consider also from the point of view of funding agencies that can do much, much more with a fraction of the money that is already available to them. That's why I am confident that this effort, once it overcomes the skepticism that awaits any outside-the-box solution to a problem, will quickly gain robust trajectory and momentum. To make this happen is my mission now.

In the next few essays, I will talk about my approach (essay 2) and provide an overview of the traditional system (essay 3) that will serve as the reference framework for the subsequent essays. I will then talk about the problems related to funding (essay 4), mechanism (essay 5), and data (essay 6) in the traditional system that I sought to address in the new system. Finally, I will talk about the fixes proposed by others, why I think these fixes would have limited impact, and the general guidelines I used for designing the new system of research (essay 7). These seven essays together will provide you the necessary background information that I think is essential for becoming actively involved in further developing this new system for research.

Cedric