

Stress in Biomedical Research: Six Impossible Things

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Biomedical research may not be *more* stressful than other disciplines, but our stress is compounded by some of the inherent features of biology. We consider six impossible things and what we might be able to do about them, provided they are believed by lunchtime or, with practice, before breakfast.

"I wish I could manage to be glad!" the Queen said. "Only I never can remember the rule."

Science, this very creative human endeavor to understand the nature of the reality that exists independently of ourselves, is impossible. By "impossible," I am not saying "very, very difficult," although it is that, as well. We use our senses and instruments to extend them to try to map reality (at least those bits we care about) onto our consciousness and perceive that the map we collectively share *is* the reality. I know I am being very Cartesian here, but hopefully you can see what the problem is: the "map" is not the reality. In *Sylvie and Bruno*, the mathematician Charles Dodgson imagined a map of a town that was enlarged to the point that it was superimposed on the town itself and asked if, even now, it served as a map of reality (he was much funnier than Descartes). The point here is that science, and this form of science that I and presumably you do, biomedical research (which I suppose is impossible *squared*), is unbelievably frustrating. And, as a consequence, stressful. The choice to be a professional biomedical researcher holds the promise of a life of rich intellectual exploration and the joys that this can bring, provided we can deal with the difficulties.

My mandate here is to identify the sources of stress in our scientific lives and to suggest ways to deal with them. At the outset, I must point out that I have no formal credentials in this regard: I am not a philosopher (obviously), a clinical psychologist (nor a patient), or a psychic advisor (thankfully, although I'm sure they are very nice, should one happen to

be reading *Molecular Cell*). But given the level of stress I seem to experience every day, I suppose I am something of an expert. That said, I urge you to ignore everything I say (and to *not* ignore it is at the reader's risk). I can only tell you what seems to work for me, and I have no idea if it can work for you.

Here are some of the sources of stress, several of which are unique to our profession, and how I try to deal with them. Each one is impossible (by which I mean "very, very difficult"), but even the attempt seems to help, and I've divided these into six impossible things. I am not sure that it is *really* six things, but the number was chosen because the White Queen asserted that with practice she regularly believes six impossible things before breakfast. Me, I'm still practicing. (If, by chance, you have no idea who I am talking about, then stop reading this immediately and obtain a copy of *Through the Looking Glass* by Lewis Carroll. Reading it is much more important for your development as a scientist than anything I can tell you.)

Thing #1. You Are Not in Control of the Answers

I contend that this is one of the greatest sources of stress in our professional lives. As scientists, we don't ask for much: we want to have some good ideas (see #2), design some good experiments, do the experiments, and have some of them work. We'll trade fast cars, flat screen TVs, big houses, and large bank accounts for even the chance of this, and *if* our experiments work, we are (albeit briefly) happy, and all is right with the world. But we know from wretched experience that most of what we try doesn't work, and this stresses us out.

There is an important reason for this failure of perfectly logical ideas to translate into results, and it will be helpful to get this out of the way first. Life is not logical, because living things are not designed. Any biological system is a cobbled-together, makeshift affair that once upon a time happened to work better than some other contraption, so that it was reproduced and subsequently built upon. All biology in this view of life is an historical accident. And it is for this reason (among others, as we will see) that our experiments so often fail. Life does not yield to logic.

So what can we do? The key is this: Control what you *can* control. Although you cannot make an experiment come out as you might like (or as logic would dictate), you can do a great deal to ensure that you get at least *some* sort of answer that will hold. If you buy a kit, a reagent, or an assay, even one you have used many times before, test it and optimize it. Do small pilot experiments to ensure that your system is working smoothly before setting up the big experiment. And plan that experiment carefully so that if it *does* work, you will be able to interpret the results. Keep careful records so that you can not only do it again, but also show someone else how to do it. You cannot control all the variables, or the outcome, but if you control what you can control, you will increase the chances that what works once will work again. And in doing so, you will reduce one of our great sources of stress.

But of course, that is only one of the problems we face in our professional lives. To do the experiments that *might* tell us something of fundamental interest, we must have ideas that have the

possibility of holding some secret that we can probe. If not, we fret that there is nothing new under the sun to discover. Where do the great ideas (even if many are ultimately wrong for the reasons we've seen) come from? Here's where.

Thing #2. Ideas Come from the Eighth Dimension

Okay, I'm not sure what the eighth dimension is, except that Buckaroo Banzai went there in a fast car. But that's where the great ideas that drive our work come from (or something like it), and because we are so often wrong (see #1), we need a lot of them. Let's be clear, though: There are many ideas that are not eighth dimensional (or great). "Let's see if our drug also works in these cells over here," might be useful, but it is not what we're talking about. To decide if it is an 8D idea, apply the coolness test—is it so absolutely *cool* that someone else to whom you tell it cannot stand not to know whether or not it is true? (Or, in other words, do you *need* to know the answer?) These are the sorts of ideas I mean. Contrary to popular notion that good ideas are a dime a dozen (or a *gazillion* per euro at the current exchange rate), they are very valuable. A great idea, in general, is worth approximately the value of a very nice grant, provided you can demonstrate that it is likely to give an answer (see "coolness test," above). So how do you get hold of such an idea? Or a dozen?

You are going to hate the answer: Read. A lot. Read everything you find interesting, inside and outside your field, and then read everything else. By "read" I do not mean look at the abstract (although that is a start) or download the PDF (ditto). If you are reading five to ten papers per day, you've got the gist of it. If you are new to this, it is very slow going at first, but you can get very fast at this, really.

Here's why this is so crucial. Creativity, as near as we can tell (I've read about this), emerges from a combinatorial process in which bits of information are rearranged and extrapolated at a subconscious level—think of it as a conceptual smoothie sloshing around in your brain. Then, when you happen to think about something you have noticed in the lab, wondered about in the literature, or worried about late at night (you do this, right?), there emerges an "aha" that *might*

explain something that has never been explained before. (How do you know it hasn't been explained before? Because you did the reading!) This only works if there is a lot of information oozing around in the blended brain smoothie. And by the way, reading is pretty relaxing, so think of it as stress relief (if reading stresses you out, it might be a good time to reconsider your career choice).

I acknowledge that many trainees are loath to be seen sitting at their desks reading, for fear that they don't "look busy." So don't read at your desk. This idea that reading is not "work" is nonsense, but you may not want to point that out. So if your supervisor asks where you were, rather than present the list of what you were reading, turn the discussion to the cool ideas you have gotten.

As an aside, this is also a very useful bit of advice for someone who is in transition—if you wonder what you can do in a short time (say three months or so) that can actually make a difference as to whether or not you will be hired into the next-level position you might desire. Read one hundred papers, really read them, and you will increase your chances of obtaining that job you might desire, certainly more than would your thoughts of initiating another project.

But this is beside the point. We are talking about stress, not jobs (although they are not unrelated). So far, our considerations have been about successful ideas and experiments, and we know that there are so many other sources of stress in our professional lives. What about those?

Thing #3. You Cannot Multitask Your Research

Wait, before you argue this point, here's the thing: of *course* I multitask. My desk is mission control, complete with pulsating screens, ringing phones, flashing lights, and "Houston, we have a problem." (Except that it's not only Houston.) Sorry, I know that most of you reading this have never actually seen a space launch, other than watching a DVD, but this is so iconic in my own experience that it goes to the heart of the multitasking mystique. (As a scientist, I hope that Ed Harris in *Apollo 13* is more your role model in this regard than Alec Baldwin in *Glengarry Glen Ross*—although both are worth a look.) But being

on top of the game can be fun and exciting: problem solved, next problem solved, orders ordered, data crunched, blots blotting, cultures cooking, bring it on!

But of course, it goes well beyond this—all of us must deal with an array of problems and solutions that have little to do with fundamental biology and much to do with business, administration, deadlines, and regulations. And we multitask these, too, in large part, because we can. The wolves circle, and we follow the (very useful) maxim that we can keep them at bay by feeding the nearest one. Do not think that we don't seek this out—it is the rare individual who does not strive for more authority and with it more responsibility and, in doing so, more demands on the limited hours of the day. "If I can just get *that* position, I'll feel accomplished and secure." And when you attain it, did you really think that there would be *less* stress? Don't make me laugh (I hope you know I wasn't laughing). This idea of achievement and security come from our academic upbringing—nail the test, ace the course, graduate, advance, follow the committee's recommendations, defend, and *welcome, Dr. You!* In other words, I bet you wish you had taken the *blue* pill. (If this reference is arcane, you need to get out more. This is, in turn, another reference. If that doesn't help, Google "Larry and Andy Wachowski, 1999," obtain the movie, and look out for the *Alice* reference after the description of the pills.) The more we do, the more we find we have to do, and the challenges multiply. Multitasking is inevitable.

But there is a fundamental problem with this perspective (and approach). It is those things that *don't* snap at us and demand our attention, those deadlineless things, that often actually *count in the long run*. Feeding only the nearest wolf (then turning to the next and the next) reduces stress in the short term, but does not relieve our existential stress, that deep concern that we are not progressing in what we got into this business to actually *do* (which, of course, is the point of things 1 and 2)—yes, we must attend to administrative matters in our profession, but to focus on these can only secure us as administrators (which is fine if that is your goal, but if that's *you*, I doubt *you* are still reading this).

Developing our ideas, thinking about results, writing up the research, planning the next stage of the research: these things take time—focused, uninterrupted time. These have to be made into wolves, too, even if they come from ourselves. Keep them near and make time, free of other distractions, for the care and feeding of these all-important creatures. You may find that the other wolves become smaller, weaker things by comparison.

I'm not saying that we can avoid the stress of all those things that demand our time that are not central to our research—we know that they are parts of the job we do. But what I *am* saying is that while it may be tempting to fill our days with dealing with administration, teaching, management, and all the other circling wolves, this must be with the conscious decision that we do not value the research we do as highly as these others. If that is not the case (and while I can't speak for you, I can say with certainty that it is not true for me), then make the time to devote to your research. I find it very relaxing.

Thing #4. Stress Can Be Good for You

Stress is a by-product of our evolutionary history, the hypothalamic harbingers of fitness (referred to as the “four Fs” in one undergraduate psychology textbook: fighting, fleeing, feeding, and mating). And while we know that chronic stress can be detrimental to one's health, a *little* stress can be a good thing. For example, there is a story about springboks (the antelopes, not the rugby team) at an animal park—despite acres to roam and mingle in predator-free herbivore heaven, they were not in prime health. Then a savvy animal behaviorist created a fenced-off area, upwind, where he housed some large cats, and the springboks now flourished, if somewhat vigilantly. And perhaps here is another, better example from the world of theater: actors know that to go on without a preconditioning period of stage fright is to risk a terrible performance. A good actor nurtures and savors the precursory jitters, peaking just before entrance.

The trick is not to eliminate stress, but to master it, bending this evolutionary gift to our needs, those times when we

need it. The last two impossible things are examples of those times.

Thing #5. Be an Athlete

I am not a runner or any sort of athlete of the physical sort, so what I am going to say I have garnered from friends who are. They tell me about a thing called “the wall,” a point at which the body simply cannot continue to sustain the physical hardship of the competition. Athletes find a way to dig deep and press through the wall; they do it by training, experience, and sheer will. What we have to do is not dissimilar (although I suspect it has a different underlying physiology)—we have to be mental athletes who struggle with difficult concepts until we hit a wall and keep thinking. And when our ideas are wrong, dashed by experimental evidence, *we keep thinking*.

Of course, the stress goes beyond this problem with ideas versus experimental reality, but the athlete idea serves us here as well. With training, focus, and the will, we can handle all the things that frustrate our efforts to succeed in this business. And when we hit the wall, we go through it. It's what we do.

Thing #6. You Are Your Support Group

If you have gotten this far, you may well be thinking, “But there's nothing here that helps me with the stress I feel in this job.” We do our best, and our work, when it *does* work, is savaged by reviewers. Or we *finally* manage to publish it, and we feel that nobody has noticed. It's so *hard*, and I have not given a single piece of practical advice as to what to do about it.

So I apologize in advance for what I am about to say: Oh, please stop *whining* and get some *backbone*! Who ever told you this was going to be easy? If you are a student or a postdoc, and you feel that the stress is overwhelming, look into some other career choice—it does not get easier. Yes, I know that we are supposed to tell you that it will all be fine if you can just keep at it, but this isn't a service industry. This is a creative enterprise that has this in common with all other creative enterprises—you do it not because it provides you with security and a stable career ladder, but *because you can't bring yourself to do anything else*.

In a short film by Martin Scorsese, called “Life Lessons” (in *New York Stories*, 1989), Rosanna Arquette, playing a young artist, abjures Nick Nolte (as the derelict but highly successful painter) to tell her if she is *good* enough to be an artist. He responds by asking her why she cares what he thinks, she is either going to be an artist or not. His opinion makes no difference at all. Science is not all that different.

Many graduate students and postdoctoral fellows and even some faculty got into this business without fully realizing how hard it is, and at some point, you may decide that continuing in this mad pursuit just isn't for you. You need to know that *this is fine*. Hopefully, you began this path because *you like science*, and if you dislike *being a scientist*, it need not follow that you no longer like science. There are a great many ways to use the skills you have acquired, both practical and intellectual, in pursuing other careers. I encourage you to explore those other options at the earliest opportunity. But if you are going to be a scientist anyway, then decide to do it. In the words of a small, green philosopher, “Do or do not. There is no ‘try’.”

So if you have made that decision, get tough and get on with it. And when you do, you may find that it becomes a habit. You might even enjoy it.

These assertions, these impossible things to subvert, subjugate, and master the stress in our scientific lives are, at one level, ridiculous—there are no simple answers as to what can lift you onto the wave so that you can ride it out. These impossible things, I believe them anyway. It is a wonderful thing, really, that our society values our endeavors enough to let us do this for a living, and that is a source of joy. And while it may not be true, it *seems* to be true that happiness (whatever we wish to call it) is a decision, not a condition. (This, I think, is the “rule” the White Queen could not remember.) So in between all the stress, frustration, and challenge, don't forget to have some fun.

Finally, one last thing: I wrote this on a very short deadline, while traveling between international meetings, and struggled with the ideas that I know do not do justice to this important problem. It was *terribly* stressful—I just thought you should know.

Okay, I'm *kidding*.