Journal Pre-proof

The easy way is hard enuff

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My Word

The easy way is hard enuff

Andrew Murray

Hell has frozen over. The world is in the grip of a pandemic that has closed down society, shuttered your lab, and threatens to cause millions of deaths and untold economic misery. You're confined to your apartment, labs that have been converted into testing sites have all the volunteers they need, alcohol supplies have dwindled, and you're discovering just how desperately you love experimental science. If someone lined up every complaint you'd ever made about boring techniques, failed experiments, and your idiot advisor and wrote each one on a large, separate piece of paper, you'd happily eat them all if it would let you back into lab to do your now beloved experiments and get on with your quest for scientific knowledge.

But even this extreme feat of mastication won't let you back into lab, so what should you do? Learn Python, write a fellowship proposal, read all those papers that you've always been meaning to digest? These are good ideas, but I claim to have a better one, which is to become a better experimentalist from the comfort of your very own couch plus everyone's favorite new medium, Zoom.

To illustrate, I'm going to call on an English Patient. I was an undergraduate in England and department that gave my degree had coffee in the morning and tea in the afternoon. At coffee conversation would run like this: "I have a great idea for an experiment to do this afternoon"; my friend Charlotte "Oh Andrew! I can see three missing controls, four reasons the

experiment might fail, and even if it works, it's unclear that any knowledge you gain from success will be worth your time and energy." Later, at tea, I would present a revised plan with the controls added and a simplified and likelier-to-succeed overall plan, but Charlotte would reply "Well that is an improvement, but I've been thinking too: I see two more missing controls and several more flaws that make your estimates of success wildly too high." And I, of course, would return the favor by using the harsh light of reason to make Sarah's proposed experiments shrivel at a similar rate. Perhaps, after a month of jousting, exactly two nearly perfect experiments would have been done, only to fail because of flaws that neither of us could foresee.

The other extreme is American exuberance, something I absorbed in graduate school. The fundamental idea is that doing more experiments means more results, that flawed experiments can be helpful too, and that stopping for tea and coffee is silly, when you can work frenetically till 10pm and still have the bars open for another four hours to discuss life and science. Like the English Patient, this is a caricature, but every scientist I know will admit that they've had this sinking 11pm sensation: "Oh fiddlesticks, I've just seen the fatal flaw of the experiment I'm about to finish that essentially guarantees that I can learn nothing from it!"

My claim is that you can hold that sinking feeling at bay and increase your post-Covid19 productivity by doing two things: dissect and critique every experiment that you've done over the last six months, and find good jousting partners to poke English-style holes in these old experiments and all the new ones that you're going to rush to do the moment your lab reopens. Their lances will force you to admit that many, and possibly most, of the last six months' failures should, at least with the perfect vision of hindsight, have been avoided. You should also be asking whether the inferences and conclusions that you drew from the experiments are really supported by the data. Again, if you're honest with yourself, you'll discover that there are logical

flaws and alternative interpretations. And if you're not, your jousting partners force you to open your eyes when you try to defend the evidence that supports your future plans.

When you discuss the experiments that you're planning to do, things are likely to be even worse. Your intellectual motivation for individual experiments, entire strategies, and perhaps your overall project will be vigorously questioned. Missing controls will proliferate like desert wildflowers after the spring rain, and convincing arguments for the fallibility of experiments that you thought were guaranteed to succeed will pop up like molehills on the parental lawn.

One especially useful group of people to talk to are the folks who run core facilities and help with data analysis. In modern science, a lot of work is done by such core facilities: for example, cell-sorting, mass spectrometry, sophisticated microscopy, and DNA and RNA sequencing. Normally, you're too busy to seek the advice of the people who run these facilities until the first and second attempts have failed and your PI is yelling at you about the cost of these experiments. But now you have nothing but time and the staff of the core facilities are in the same boat. Ask them to look over your plans, tell you what quantity and purity of material are needed to produce the data you need, and critique your calculations and assumptions about how your experiments will produce that material.

Doing everything I've advocated will take serious time and effort and it won't be as fun as learning Python. As your plans for your first three months back in the lab and your expectations about what they will reveal shrink, the initial effect on morale may not be positive. But pain and suffering now should have a dramatic payoff in the halcyon world when experimental scientific research begins again. Ask an experienced experimentalist what fraction of their experiments either made it into a paper, or were directly necessary to produce the data in the paper: their answer will be between 5 and 10%. Imagine that three months of rigorous self-

flagellation might increase that fraction 1.5-fold, that you will be working at the bench for another eight years, and that it takes two years of work (the optimism of scientists never dies!), at your pre-pause level of productivity, to make a paper. As things were, you would have produced four papers, but if you become 50% more productive, you will, instead, produce six papers. In retrospect you might even think that the three months that you spend in this socially distanced, Zoom-filled hell, were the most valuable ones of your scientific life.

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In Brief:

Andrew Murray argues that you can use your forced exile from the lab to produce better future experiments by dissecting your past failures and successes and collaboratively critiquing the experiments you're planning for your return to the lab.