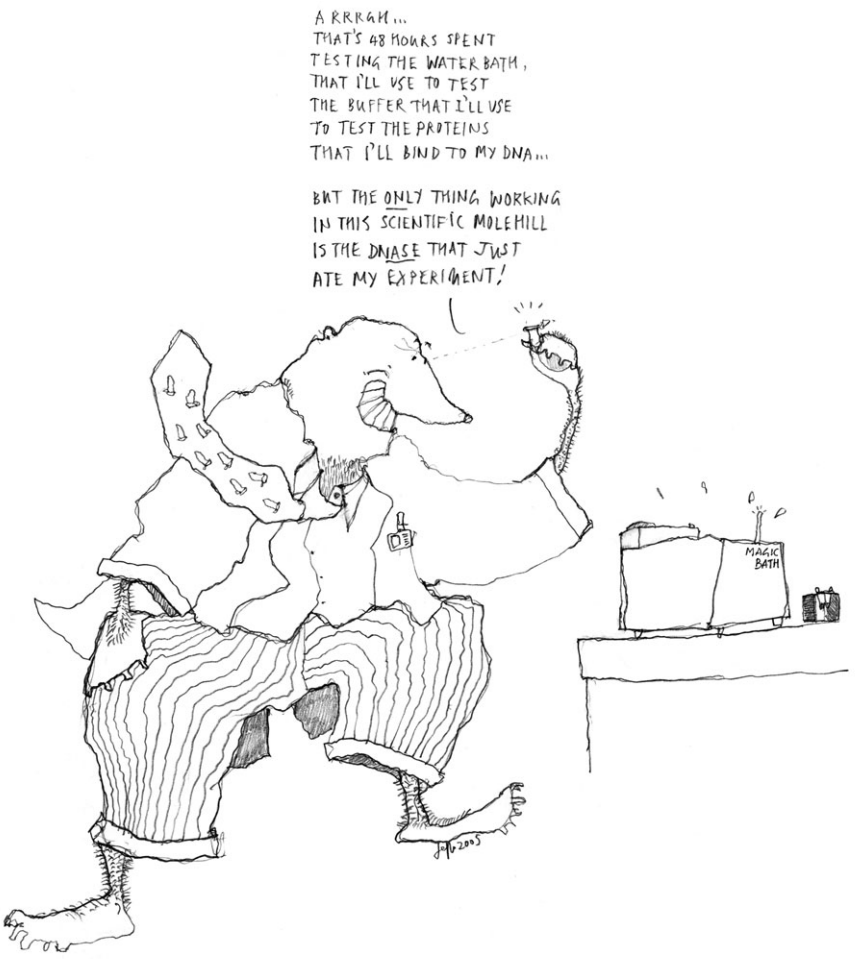
Journal of Cell Science

An occasional column, in which Mole, Caveman and other troglodytes involved in cell science emerge to share their views on various aspects of life-science research. Messages for Mole and other contributors can be left at **mole@biologists.com**. Any correspondence may be published in forthcoming issues.



The opposite of eureka I: nurture

Monday morning. Strong coffee, read the paper (the *news*paper, it's Monday), brace myself. Deep breaths and procrastination (maybe just one more cup of coffee). Time to face the music.

The weekend is over, and it is time to look at the crestfallen faces of all the Molets in the lab whose experiments not only failed, but failed on the *weekend*, thus reminding them so unkindly of what else they might have been doing to the same, ultimate experimental result.

What hurts more than a failed experiment from which nothing at all can be learnt (except that something is horribly wrong)? The mind leaps to thoughts like this: "Instead of spending the past 48 or so hours cooped up here, I could have been lounging on the deck of a fabulous yacht, sipping cocktails carried by gorgeous servers, while we gazed on the turquoise waters of where it is that I was *not*. And I'd still be just where I am now, only happy." Technically, according to the laws of logic, if/then statements are automatically true when the 'if' part is false: "if my experiment hadn't failed miserably, I would have instead just spent a weekend on some fabulous yacht" is logically true, but don't ask me why. It definitely *feels* true, though.

Experiments fail. It's a fact of science and a fact of life. In the facts of life category, here's one that always fails for me: go into a store to buy a gift without knowing what I'm going to buy – inevitable failure). But in science, experiments fail for a variety of reasons, and in biomedical science, the reasons can be so profound that it is amazing that things ever actually work. But we'll get to those profound reasons later; first, let's look at some relatively easy ones.

Think back to your lab practical days (for those of you who might be reading this who never took a laboratory course, I have this to say, "What in the world are

you doing reading *this* ? Go outside and play. You need the sun.") Those were those horrid courses where you were instructed to perform an 'experiment' for which the answer was already known (or readily calculated) and you were given a set amount of time in which to get that answer 'experimentally' with the deviation from the expected results determining your grade. (I was honest, and therefore got terrible grades, like the time we were supposed to determine Planck's constant and my answer was 'noxious smell'.) And I *detested* those vermin who fudged their results, 'fudged' being a nice term for 'faked'. But they got great grades and learnt a valuable lesson in the performance of scientific research (yes, I'm being sarcastic). Maybe you liked these courses (in which case, you too need to go play outside). I hated them, even the chemistry class in which we performed so many ether extractions that we ended up sitting on the floor giggling over how hopeless our measurements were (these were less enlightened times).

But I digress. The simple and obvious point is that even when we know the result of an 'experiment' in advance (hence the quotation marks I have been using so annoyingly), they can fail for simple reasons of technical inexperience. There are a number of procedures we do routinely in my lab that rarely work the first time they are learned by a new Molet, but work reproducibly once performed a few times. These are among the easiest failures, which, while frustrating, evoke a knowing "Do it again, it'll work."

A second class of experimental failure is similar, but can apply to anyone, even the most experienced bench scientist. These are failures as a consequence of random variables, which is the way we scientists say "crummy luck". Any experiment worth doing is a complex process, and as we know, complexity generally invokes some level of chaos. A butterfly wing-flap on a beautiful South Pacific island (where you *would* have been, had your experiment not failed), etc., etc. You know, chaos. A bit of dust, a puff of air, a sudden attractive distraction at the wrong time – something goes wrong just this once. And the experienced among us know to just do it again, with a shrug and a "it happens." Minimizing chaos is what we do, but we can't do it all the time. (As for me, my desk is approaching entropic heat death, but that's just me).

There is a third source of failure that is an uncomfortable one, but as with the first two, not terribly interesting. But it is disturbing (for us withered old folks) and becoming a more important source of failure than the first two (which are solved simply by 'doing it again'). You bought an antibody, a reagent, a kit – and it didn't work. Of course, you won't know that this is why your experiment failed until you've spent about a week (or more) checking every antibody, reagent, and kit that contributed to your massive experimental undertaking, whereupon you discover that the culprit was a commercially obtained thingie that doesn't do its thing, despite aggressive advertising to the contrary.

Why is this so prevalent? Surely, no respectable purveyor of quality merchandise for the research community would intentionally (or even unintentionally) sell us something that doesn't work: that goes against the central tenets of capitalism and the force of the marketplace (for an American, like me, tantamount to heresy). But sadly, this is so, and it is becoming decreasingly uncommon (it's a sad thing, which is why I used the embedded double negative to try to cheer you up).

It is worth taking a moment to see why this is so, which will lead us to undertake the only way we can go about avoiding this important source of failure. Companies produce reagents and kits to sell, and if they never work at all (or only rarely) the company will eventually cease to exist. Usually this ensures that, at least at first, things work – a reagent begins its commercial life as a useful (or moderately useful) commodity. (Some reagents are notoriously useless from the start, and it seems that it is entirely by the force of advertising that they continue to be used, thereby contributing either directly to failure or to the constant trickle of published artifacts.)

But good reagents often go awry, and the dependable kit can suddenly become the nail for which the battle was lost. There is a fundamental reason for this. Individuals who succeed in making useful reagents of excellent and reproducible quality for a company are generally rewarded by being given the more interesting task of making *new* products; the job of keeping up the quality of the old ones falls to others who are not always as conscientious as the originator. Quality declines. Experiments fail.

There is a simple lesson here, proving the maxim that even a terrible experiment has value if only to serve as a bad example (we have many of these displayed around the lab with appropriate and often funny labels, such as "boil your probes!", and these have the added fun of causing utterly confused looks on our non-science visitors). It is this: test your reagents *before* you use them in an experiment. A good experiment is a hugely expensive undertaking, expensive not only in terms of reagents and time, but the tremendously precious commodity of expectation. We *expect* a well-designed experiment to yield useful information (hence the investment of reagents and time); when they don't, we lose momentum. We stop loving our question and it becomes an albatross around our necks (data, data, everywhere, and not a byte to eat – sorry STC). Yes, it's boring to test each reagent in simple assays, determining optimal concentrations and procedures for each new batch of even our trusted reagents, but in doing so we can greatly increase the chances that the all important experiment will work (and work repeatedly). Untried experiments, crafted in our imaginations, are infants. We have to test their food and the temperature of the bathwater, and protect them from the cruel world around them. Nurture them. Because when they *do* succeed, we are so proud of them, and we can't wait to show pictures of them to our friends and even total strangers.

To this point, however, we haven't talked about the most insidious reason why experiments fail. A reason that is at once terrible and wonderful. But not right now – I've been avoiding facing the Molets...

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