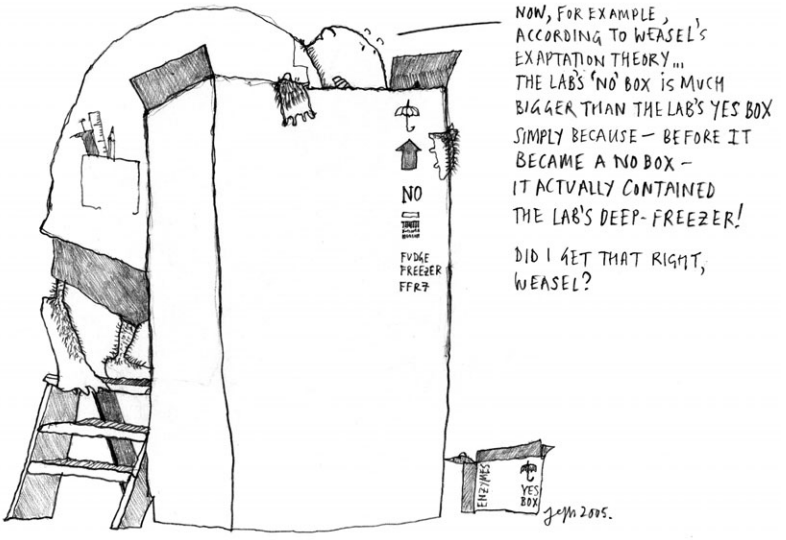
Journal of Cell Science

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 II: nature

The American philosopher and one-time riverboat captain Samuel Leghorn Clemens once wrote, "It is best to prove things by actual experiment, then you *know*; whereas you depend on guessing and supposing and conjecturing, you will never get educated." Wise words. But then, he didn't have to get his experiments to *work* in order to publish; he just published. He was Mark Twain, of course, and he dealt with failure in his investments not his research.

Why do experiments fail? If you were with us last time you'll remember that we talked about the easy reasons: inexperience, bad reagents, and sometimes just bad luck. Up to now, though, I've avoided the most dastardly reason of all: in biomedical research, especially, we are often just plain *wrong*, and the reason is interesting and important. Hermann Weyl, the physicist, described just how wrong we can be, like this: "Allow me to express now, once and for all, my deep respect for the work of the experimenter and for his fight to wring significant facts from an inflexible Nature, who says so distinctly 'No' and so indistinctly 'Yes' to our theories." And he was a physicist. We in biomedical science often get nothing distinct from even a perfect (or perfect-seeming) experiment.

We have come, finally, to the most frustrating, confounding, and downright interesting reason that not just experiments but entire projects fail, and it has to do with how nature is patched together. To design experiments, we envision not only how things *might* work, but how they *should* work. We expect the system we are studying to display what we often consider to be hallmarks of natural processes: a simple logic, an economy of design, an elegant simplicity. Often we know how the system must work, and use experiments to prove it to others. And that's why we fail. Because not only doesn't nature care about such things as elegant simplicity, but it doesn't even care if there's a better way (in theory) than what happens to be used to make something work.

Of course, by "nature" I mean evolutionary processes, the understanding of which provides what may be only useful theoretical tools for the elucidation of biology, how it came about, and how it fits together. And by "care" I mean to give the appearance of caring, despite being non-conscious – like a thesis examiner. Surprisingly, many professional biomedical scientists have at best a rudimentary grasp of evolutionary theory, but then many professional biomedical scientists are not very good biologists. A real understanding of evolution is a tremendous asset (I certainly do not pretend to be competent, but I greatly value my ongoing discussions with those who are, not because they can help

me get my experiments to work, but because they can help me understand why they don't, which is something.)

I wanted to find a useful analogy to explain the principle I am struggling with here, and it was my good friend Weasel who provided it. Yes, despite what you've heard to the contrary, Weasel and I are great pals; we only pretend to detest each other in public so that editors will ask us to review one another's papers.

When I posed the question of why experiments fail to Weasel, he gave me this, which I am happy to pass onto you (I am paraphrasing here; Weasel's eloquence in verbal dance far outshines my own, and he uses lots of arcane words that I've since forgotten. And he's much smarter than I am, though I'm better looking.)

"Remember the film Apollo 13, that remarkable movie that managed to sustain tension to the end, despite the outcome being dictated by recent history? At one point, with the astronauts in bad trouble up in orbit, the engineers on earth were given the job of providing a working solution from the bits and pieces available to the crew – some cardboard tubes, bits of metal sheeting, and other odds and ends. If the problem couldn't be solved using what was available, then they were going to die. (If you want to know what happens, read the book, or, better, watch the film, because it has better visuals).

"That," says Weasel, "is what evolution does. Faced with an environmental life-or-death problem, the available genetic odds and ends are patched together and if one particular arrangement happens to work to advantage, the individuals that have it survive to reproduce. It doesn't have to work well, it doesn't have to be elegant, it only has to work better than what else might be available, and it will stick. And any improvements, modifications, or solutions to other problems will have to be patched in around this jury-rigged mess."

Weasel is beautifully describing the process of exaptation, which has been explored in detail (and far more eruditely than I could hope to do) by the late Stephen J. Gould, who is sorely missed. Exaptation is the process whereby a structure (for example) that has been selected for one function takes on a different function to which it seems (by hindsight) suited but which could not have otherwise so evolved by incremental steps. Gould called this the "5% of a wing problem", because a proto-wing could not have afforded flight unless it was already nearly perfect, and therefore evolving *for* flight appears impossible without positing an external agency (akin to magic). The solution, in the case of wings (and probably feathers as well) is likely to relate to thermoregulation: feathers and even tiny wings provide an excellent method of controlling temperature, and only when of sufficient size (and perhaps through other functional iterations) might they have become useful for flight.

It is a small step to take this view of exaptation and its consequences to the realm of the molecules and cellular processes that are the purview of the biomedical scientist. Molecules were not necessarily selected for the jobs we think we see them doing now any more than duct tape on board Apollo 13 was there to create an oxygen conduit. If a molecule with one function happens to patch into another function (say, by happening to stick to another molecule), and it does something vaguely utilitarian, we may simply be stuck with it, not only for now, but perhaps forever more.

Here's an example. In the mitochondria of brewer's yeast, there is a relatively small molecule that has the job of feeding electrons into the electron transport chain. In *us* this is the function of a tremendously complex set of some 50 proteins that we've called Complex I (to show how complex it is). Of course, this must mean that electron transport in animal cells is vastly superior to that of yeast and functions under a range of conditions that are inaccessible to the simple yeast protein. But as it turns out, the lowly yeast protein works just fine in yeast, and even more amazingly can substitute for Complex I perfectly well in animal cells. "Aha," you say, "but we're more complicated! It must be that we *need* those fifty odd proteins for our complicated lives." So you design an experiment to show that even if the little yeast protein can work in some of our cells, it isn't really enough to replace Complex I in us. I don't know if you'll succeed in proving your hypothesis, and neither do you, even though we might both agree (for what it's worth) that all those proteins are there in us for some reason that can't be replaced by just one. Because it is also possible that we're simply wrong. Maybe, in the dark recesses of time (*way* back, even before PubMed), the bit of goo that would become animals didn't have this yeast protein, but managed to slap together something that worked anyway (even though we needed more and more proteins to make it work better). And we're stuck with it. As a consequence, all of our assumptions and insights may well wash up as so much flotsam on the shore of experimental result.

Transcription factors and glycolytic enzymes may double as cytokines. DNA repair molecules might communicate with cytosolic proteins and alter their functions. Molecules that control mitochondrial membrane stability may also play independent roles in the cytoskeleton. And these may all be incidental or coincidental, rather than profound, or they may be profound: we don't know. But life wasn't engineered, and we can't decide how it *must* be, only how it *can* be. Unfortunately (or perhaps most fortunately), life just happens, however it can. (There is a fascinating and important area of investigation into how life and other complex self-replicating systems *must* be, but that's a subject for another time.)

This is the problem then. Any attempt to apply logic to such a system *may* yield success, but in no way is it guaranteed. So on Monday mornings, when I meet my Molets, and confront their hurt visages, I cheer them with tales of make-shift nature, and our joint adventure in finding out how it *can* be put together, and how it *is*.

Also, it helps a lot of I bring breakfast.

Mole

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