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An occasional column, in which Mole and other characters share their views on various aspects of life-science research. Correspondence for Mole and his friends can be sent to **mole@biologists.com**, and may be published in forthcoming issues.

Revolution II – You better change your mind instead

Blossoms blooming. Heads all empty and I don't care. Except I do. Care. (Sorry, just groovin' to some hippie music.) If you are just joining us, we've been sitting in sunshine, in the Age of Aquarius, talking about what the *Man* is doing to biomedical research funding and the need for revolution.

People, come together now. We, the scientific community, are being *managed*. The agencies and foundations that support research have decided that we are much too wrapped up in idle navel-gazing and instead need to be better controlled if anything good (and by good, I mean useful) is to come out of the research effort. Forget 'bench.' Give us 'bedside.' Put away your pipettes and Petri dishes, your animal models and your complicated theories, and go *cure* something. Get with the program, or forget about funding.

"But wait a minute there, Mole!" you say, "I *do* want to cure disease; that's why I got into biomedical research in the first place." (Okay, maybe you aren't saying this, but your friend at the next bench is.) "If we have to divert some funds and submit to a bit of management, it will be worth it if it means we affect some cures!" (Maybe you said "*effect* some cures" – I may have misheard you.) And yes, you would be quite correct if it would, indeed, result in more cures. But sorry, you're wrong, and I can prove it.

As we discussed last time, there is a massive international effort in translational research next to which our small, government- (or foundation) supported efforts pale; this is the global pharmaceutical industry. And collectively, this global enterprise produces, on average, about four new drugs each year, approved for use. Converting *all* research money for basic studies into such a translational effort would not significantly increase this number, and would ultimately (I would argue) diminish it.

Clearly there is something wrong with the way we convert hard-won snippets of biological insight into practical applications that make their way into the bodies of patients who might need these applications. Currently, there are two major proposals to make this work more quickly and efficiently: (1) Make it much easier to have a drug approved (that is, relax the restrictions on approval) and, (2) apply the business model of the pharmaceutical industry to basic science. We talked about the second last time: this is the model that gives us four drugs a year at fantastic expense – how is this the right way to go?

With respect to the first, I need to tell you a story (it's short). Once upon a time, a handsome, young Mole was hired (at a pretty good amount of money, thank you) to teach sales people at a major pharmaceutical company about the

science behind their products. All went well until one of the head executives (I think his position was 'honcho') asked about a particular drug, which I *knew* was not in the marketplace, because it had been well known for many years that it simply didn't do anything. But, the honcho informed this young Mole, it is a *very* successful drug in one particular country that has more enlightened policies regarding drug approval – it is up to the doctors to decide whether to prescribe it, and we provide the doctors with ample reason to do so. Now, he went on, could you explain to us how it *might* work to cure this rather long list of chronic diseases? The young Mole refused, lost the lucrative teaching contract, but won the Princess and now lives happily ever after.

Okay, the last part isn't true, but the rest of it is (the country in question subsequently tightened their regulatory rules and the drug disappeared from the market). And there's the rub. The pharmaceutical industry has, as its single-minded goal, the mission of effectively translating knowledge of biomedicine into effective treatments but, to a great extent, this effectiveness is carefully regulated to ensure that drugs are, in fact, effective. Because the real mission of the industry is to make money, and if this can be done with ineffective drugs, it most certainly will be. (The above story is only one case in many – most major pharmas have entire divisions devoted to less-regulated 'natural' products, which are not regulated as drugs but, rather, foods. Sure, some of these might actually contain things that have beneficial effects, but there is no system that monitors whether the 'drugs' that are sold actually *contain* any of these things they are meant to contain. But that's a discussion for another day – they are sold because they make money.) Making money is not a bad thing – it is the way of our society, but our society also insists on getting its money's worth and, therefore, the need for regulation.

"But Mole", you might say, "the system is *so* regulated, that many really good drugs are not getting to the patients who need them!" There may be something to this, and scrutinizing the regulatory agencies that evaluate new drugs may be warranted. But will this actually give us a faster, more efficient pipeline? Look, we know that many of the drugs that *are* approved are only mildly effective – at best, this approach will only give us a larger number of minimally effective treatments. This isn't the answer.

So, I argue, we need a revolution. Changing the game at the regulatory level is not going to give us better translation, and neither will applying industrial management approaches to publicly funded research. But we need something, and if we do nothing, the pressure from the public will move us in these directions. And as these are not the *right* direction (by 'right', I mean 'correct'), only more frustration will follow.

And the frustration is definitely there. My dear dad is a *big* supporter of basic research (by 'big', I mean 'enthusiastic', although he certainly also contributed to basic research when he bought me a used car when I was a graduate student). But even he now regularly calls me to say, "oh look, someone cured cancer, in mice, *again*." The public widely support the biomedical sciences, but also widely hold to the idea that we, the scientists, are failing miserably. And *we let them believe this!*

I think that the reasons there is a disconnection between basic and applied biomedical research are several. If we are going to have a *real* revolution in affecting cures, we need to look at why this is so difficult, and more, why it's so difficult to communicate our success. Let's break it down.

By the time it gets to 'bedside', it's old news

When I was a graduate student, we were going to cure diseases with monoclonal antibodies. This was *hot*, and departments recruited young investigators who could make these wonderful things. Lots of awards were handed out for progress in this area. By the time I progressed to having my own lab, we were pretty skeptical that this was the way forward and, within a few years, any suggestion that we should pursue this approach in basic research was met with ridicule because it was such an *old* idea (with no tangible success). Then, years later, drugs started to appear that were monoclonal antibodies (there was a *lot* of work to do), and some of these work fantastically well. And while there continues to be a great deal of progress in effectively developing such drugs, the technology behind monoclonal antibodies isn't being trumpeted. The public should be thrilled with our progress but we don't make a big deal about it, so neither does it. This is one source of the disconnect – the things we think are *really* exciting are so far away from their application, that we don't get much credit for what we, as a community, have actually *done*. We have to change the way we think about scientific progress; the path from bench to bedside is often *very* long, and many of the steps are, well, boring. Instead of focusing only on what's new and exciting, we have to recognize that the intermediate steps are just as important as the first ones. Alexander Fleming is widely known as the discoverer of penicillin (and was nominated as 'Man of the Century' in several polls in 1999); but where would we be without Ernst Boris Chain and Howard Florey? – if you don't know who they are, go and google them *right now.*

No, this won't solve the problem of why progress is so slow, but it does underscore that we don't pay attention to the real progress we do make. And maybe it is this slow because it *has* to be – the problems are simply much, much more difficult than we let on. We'll come back to that.

Maybe our math is wrong

All of my arguments, so far, are based on the arithmetic that goes like this: All global efforts in biomedical research = four new drugs per year. As far as I know, this is correct – or close enough. But if we consider that it takes anywhere from 15 to 30 years (based on penicillin and monoclonal antibodies) to effect this translation, *the new drugs we're seeing are the results of basic research in the 1990s*. During the early 90s, funding for basic research, worldwide, was abysmal. It wasn't until the late 1990s, into the first years of the next decade, that funding for basic research substantially increased. If, instead on focusing on drug approvals, we look at the numbers of drugs in current trials, that number has increased proportionately to the increase in basic research support ten years previously. I strongly suspect that we will see a dramatic increase in the numbers of approved, effective drugs and treatments in the next few years. So here is the very real danger: if we allow the powers-that-be to get away with dampening basic research in favor of other approaches, it will *appear that they are right to do so*. And the consequences of these actions, already underway, won't be seen until the progress dries up ten years from now.

Science is seen as too expensive

This is the notion that underlies many of our problems. Biomedical science, in fact, is remarkably *inexpensive* compared with other social enterprises. But health care is fantastically expensive, and that has led to this impasse – the fallacy lies in thinking that if we 'remove waste' at the basic level, making the transition to application more efficient, we will cut the costs of health care. This reasoning can best be seen in how I first learned the principles of capitalism, from my roommate (at the time) who sold ice cream from a truck during the summers. He bought one of his treats at a wholesale price of one penny and sold it for ten; when his costs doubled to two pennies, he doubled his price to twenty – then, later in the summer, when his cost went back down to one penny, he passed the savings on to his customers by charging only nineteen cents. I was foolish not to see the logic in all of this. Simply put, we will not reduce the cost of health care by any cost-cutting efforts at the front end.

Biomedical scientists are among the most hardworking, altruistic, cost-effective people on

the planet. We work very long, hard hours because we are driven by the most difficult questions we can ask, and we do this in return for minimal recognition by a small group of peers and for the satisfaction of getting even a glimmer of an answer to our questions. We desperately want to see our work *mean* something, and hope that we will live to see benefits emerge from our labors. I've never met a basic scientist who is in this for the money. Too expensive? Please.

But none of these are the most important reason why science takes so long to make its way from bench to bedside. There's another reason, and it's the bomb. I'll tell you all about it next time. Because right now, there's some tunes I have to listen to, and maybe I'll go swimming naked because, hey, that's what we hippies do.

Mole

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