Ambition, surprise and delight: necessary lessons

Henry R. Bourne

I first learned why we do experiments when I was already a faculty member, after four years of laboratory work.

One morning in 1972, the grey-haired fellow sitting next to me on the commuter bus turned out to be Gordon Tomkins, a biochemist I had not met, whose laboratory was in the same building as mine. I tried to impress him with an account of my measurements of cyclic AMP and adenylyl cyclase in human white blood cells. Others had assured me that studying this sexy, new hormonal signal in a human tissue was sure to bring me academic fame and fortune.

Gordon heard me out, and then said his laboratory was using genetics to unravel the actions of hormones and cyclic AMP in mammalian cells. I had to confess, I didn't know what he was talking about. Indeed, at that point, I had never heard a laboratory conversation that touched on genes, genetics, DNA or even evolution.

"It's really very simple," Gordon replied. He described S49 lymphoma cells, a cultured mouse line whose cells die after exposure to a cyclic AMP analogue. His laboratory had isolated mutant cells that didn't die, and found that they lacked activity of an enzyme, cyclic AMP-dependent protein kinase (PKA). From this, he inferred that cyclic AMP kills normal S49 cells by stimulating PKA.

Because biochemists had already shown that PKA mediated several effects of cyclic AMP in other cells, Gordon said that this role of PKA in S49 cells was no surprise. But now, he hoped, S49 cells might help us discover the mechanisms that hormones use to stimulate cyclic AMP production. Would I like to identify which hormones increase cyclic AMP in S49 cells?

I jumped at the chance. Waiting for the bus, I had known how to measure cyclic AMP. Gordon was about to show me a new way to do science.

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As we expected, adrenergic catecholamines and cholera toxin—which stimulated adenylyl cyclase in white blood cells—also elevated cyclic AMP in wild-type S49 cells. The same agents killed wild-type S49 cells, but did not kill resistant, PKA-deficient cells. Nice, but not surprising. Then, to my astonishment, catecholamines and cholera toxin increased cyclic AMP sixfold more effectively in PKA-deficient cells than in wild-type cells.

This result delighted Gordon because it suggested a negative feedback loop in S49 cells—"Somehow cyclic AMP has found a way to decrease its own accumulation." Indeed, we went on to establish that treating wild-type, but not PKA-deficient, cells with hormones or with the cyclic AMP analogue elevated activity of a cyclic AMP-degrading enzyme, a phosphodiesterase. This effect was blocked by inhibiting protein synthesis, showing that PKA in wild-type S49 cells mediates cyclic AMP-dependent induction of the phosphodiesterase.

Why, I asked Gordon, did he find this result so much more exciting than the PKA-deficiency itself? "It's a surprise," he replied. "Explaining a surprise can tell us something new about how nature works. Finding exactly what we suspect beforehand just confirms prevailing wisdom." The new result was exciting because we had not imagined it before the experiment.

I had never heard anybody talk this way, or watched a scientist hoping to be surprised. Instead, the experiments I had seen were designed to show that a particular idea about a natural mechanism was right. Failure to confirm my National Institutes of Health (NIH) laboratory chief's notions about brain neurotransmitters had proved a painful disaster. The one true laboratory 'surprise' in those years had turned out to be wrong, adding yet another failure to my record. More recently, I had been inordinately pleased that cyclic AMP measurements in white blood cells showed pretty much what everyone expected, mightily pleasing journals to which I submitted the results.

Now, finally, I had learned something truly new—it is not only permissible, but often essential, to do experiments whose results you can't predict beforehand. If you are sure that you know what an experiment will show, it may not even be worth doing. This new lesson changed everything.

I have been shy about confessing this story to fellow scientists, who usually ask, "How could you have thought this way at the ripe age of 32?" Perhaps I was unusually ignorant, but it is also true that no one had ever taken the trouble to talk to me as directly as Gordon did. Moreover, I suspect that even today many bright non-scientists, many beginners in the laboratory and a few mature scientists still think science works pretty much as I thought it did back in 1972.

In the process, Gordon taught me a more subtle lesson, about the limitations of ambition as a motivator of research. Measuring cyclic AMP in white blood cells was a good career move, but in the long run vaulting ambition by itself would not have been enough. Instead, the real pleasure in doing experiments depends on a genuine delight in understanding nature. I shall always be grateful to Gordon for showing me that delight is both possible and necessary. The motivations of most scientists, like mine, oscillate constantly between poles of ambition and delight. Perhaps a few geniuses sustain themselves on delight alone, and a few others may derive sufficient satisfaction from gratified ambition. The rest of us strive constantly to balance and reconcile the two.

This essay is condensed and modified from a chapter of his personal memoir, Ambition and Delight (XLibris, 2009).