One more thing...

How an extra control experiment led to a change of research field.

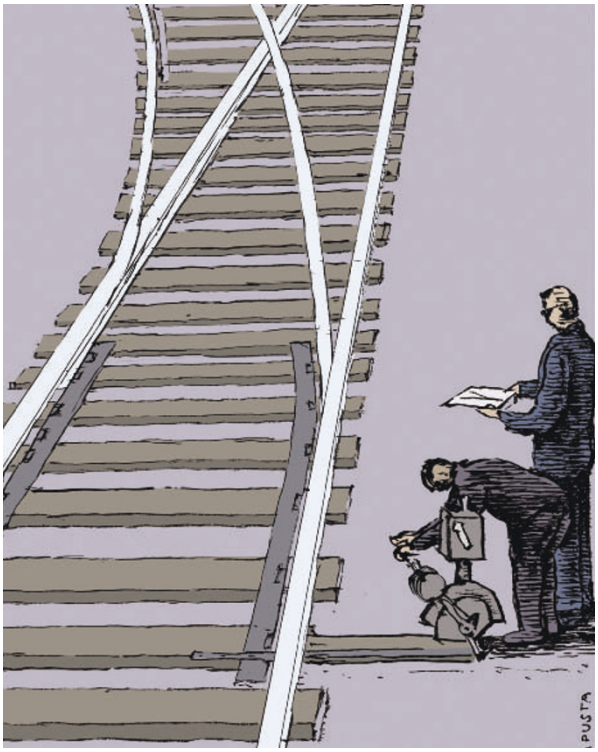
Nancy Rothwell

The excitement of an important scientific result and the satisfaction of preparing the data for publication is often tempered by critical analysis of what is missing in the story. There always seems to be that one extra control experiment that you know has to be done, not least because the referees will ask for it after you submit the paper. It's the one that will be uninteresting and time consuming, and is often left until last. It was one such control experiment that completely changed the direction of my research.

I trained as a physiologist, and my early research career investigated the mechanisms of energy balance regulation in mammals, the role of thermogenesis in energy homeostasis and the disruptions that lead to obesity. Moving north to the University of Manchester in the late 1980s meant establishing an independent research group for the first time. I had already conducted some studies on cachexia (the wasting condition that accompanies severe disease and injury) and on the role of cytokines such as tumour necrosis factor-α and interleukin-1 (IL-1) — although immunology wasn't really my cup of tea, I found these molecules fascinating.

The University of Manchester had a strong reputation for research on experimental and clinical aspects of injury, so I set up my modest lab and embarked on establishing collaborations with relevant scientists and clinicians, with the goal of discovering the causes of cachexia — and perhaps even identifying new treatments (ambitious in hindsight, but not at the time).

One of the first of these collaborations was with a recently appointed lecturer, Celestine O'Shaughnessy, and began — like so many fruitful collaborations — because we had adjacent offices and got on well together. Celestine's background was in neuroscience, which was then a mystery to me. She was working on experimental cerebral ischaemia (stroke) in rats, an area very different to my own. But it was well known from clinical studies that brain damage causes a marked hypermetabolic state and often leads to cachexia. So we got together — a good collaboration of complementary expertise — to ask if ischaemia does induce hypermetabolism, and how.



Controls and career tracks: where will that extra experiment lead you?

The work went well and we published several papers demonstrating a significant increase in metabolic rate and accompanying hyperthermia in response to cerebral ischaemia, which was dependent on activation of the sympathetic nervous system. Celestine took on a new PhD student, Jane Relton, and we planned further studies to specifically investigate the role of IL-1 in responses to cerebral ischaemia, and its actions in the brain. But events took a different turn when Celestine was seduced by an attractive position in the pharmaceutical industry. I was left without my neuroscience expert, but with a newly acquired PhD student.

Fortunately, Jane was experienced in working on the brain, and completed many experiments, showing that blocking of endogenous IL-1 by administering a naturally occurring IL-1 receptor antagonist (IL-1ra) to rats prevented the increases in metabolic rate induced by a stroke. Others in my research group showed similar effects of cytokine modification in animals exposed to peripheral infection or injury, and we identified several downstream mediators of IL-1 action. All was going well.

As we were writing up Jane's experiments on IL-1, we knew that there was an extra control experiment that needed to be done — to check that IL-1ra was specifically influencing hypermetabolism, and not directly altering the damage caused by ischaemia. This was a time-consuming study, and of course we knew the outcome — IL-1 could not contribute to injury within the brain, which was believed to be barely influenced by events or mediators of the immune system (the brain was considered be be an 'immune-privileged organ'). But we were surprised by the results. IL-1ra reduced the damage by well over 50%, and did so consistently. Still barely believing the results, we completed further experiments and published the work, but it raised little attention at the time — probably no one else believed it either.

This presented me with a dilemma. I believed (even if not many others did) that this was an important observation, which challenged the prevailing dogma of the brain as an immune-privileged organ. The problem was how could I, as a newly independent scientist with little more than undergraduate knowledge of neuroscience, take forward a project on cerebral ischaemia? I was still young enough to believe that everything is possible and that I should follow what my instinct told me was an important finding. Jane continued with her experiments, and others in the lab diverted to IL-1 and stroke, while I avidly read the neuroscience literature and went to every meeting on stroke-related research that I could. I was reassured by colleagues in industry who said that you can change fields and become re-established in quite a short time. But this was a difficult decision. I was established in the field of metabolism, had made some inroads with immunology, but had little experience in the field of neuroscience.

Enthusiasm prevailed over logic and we launched into research on stroke and, just over a decade later, we have completed the first small clinical trial of IL-1ra in stroke and are beginning to uncover the mechanisms of IL-1 induction and action in the brain. But I have not abandoned my interest in metabolism entirely, and I no longer know what to call myself. Am I a physiologist, neuroscientist, immunologist or endocrinologist?

This experience taught me two things: do the important control experiment early, and follow your intuition and enthusiasm — even if it's wrong it will be more fun. ■

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