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An open mind to narrow the gap

An unpopular, ideology-driven war between East and West; a spacecraft returns startling pictures of a planetary moon; double-stranded RNA and DNA are shown to stimulate interferon production and thereby block virus infection. The year was 1970, and such was the time: the Vietnam war; Apollo spacecraft and pictures of Earth's moon; and a scientific paper published over three decades ago this month (*Nature* **228**, 27 (1970)) describing the ability of T4 coliphage DNA to stimulate interferon production, including a remarkably prescient hypothesis about why virus-encapsidated DNA but not naked DNA could stimulate interferon production. Given the importance of the interferon response to viruses, one might wonder why 30 years passed before direct evidence was published identifying the Toll-like receptor for DNA (TLR9; *Nature* **408**, 740 (2000)). Several factors help to explain this, of course, but less often considered is that new ideas often take time to become accepted by the scientific community. On this thirty-fifth anniversary of the paper by Klienschmidt *et al.*, it is worth considering if or how much our present beliefs or biases about how the immune system responds vigorously to pathogens without inducing '*horror autotoxicus*' might be holding back progress.

The idea that viral nucleic acid can stimulate interferon production was not new. Synthetic double-stranded RNA and RNA isolated from mycophages (from a fraction originally called 'statalon') had been shown to have interferon-stimulatory capacity. The ability of purified DNA to do the same, however, had not, which was something of a paradox, as DNA-containing viruses were known to have this property.

So what was different about isolated DNA? As Kleinschmidt and colleagues reasoned, the explanation for the discrepancy was that "DNA very likely does not reach the inducer recognition site." This explanation was inferred from three experimental results: phage particles "bereft of DNA" could not induce interferon; extracted phage DNA induced little interferon; and whole phage particles induced large amounts of interferon. Their conclusion was that "DNA is the component molecule of the T4 coliphage responsible for induction of interferon and that this is made possible through the delivery of the T4 DNA in the required configuration to the inducer recognition site, implemented through the encapsidation of the DNA in the intact phage." One can only look back at this enviable display of hypothetical-deductive reasoning with delight, as we now know that double-stranded bacterial (or phage) DNA binds to TLR9 inside the cell in endocytic vesicles, its 'inducer recognition site'. But why did it take 30 years to demonstrate this?

Certainly, one important factor was the inherent vicissitudes of biomedical research. Another was that evolution of technologies required for such analysis proceeds only so fast. However, given the idea of scientific progress as being determined in part by bias, perhaps it is not too much revisionist history to consider how much the delay in the discovery of TLR9 might have been influenced by prevailing bias of the time. Consider the present well accepted paradigm of innate receptor signaling. Thirty years ago, immunity was surely conceived more linearly, as a unary response from stimulus to lymphocyte killing or antibody secretion. The present paradigm, however, invokes a binary response orchestrated first by a nonclonal innate immune signaling system, on par with the one the lowly fruit fly relies on, and second by the mighty adaptive T and B cells. The evolution of the binary paradigm must have been controversial and was therefore slow to be adopted into the background of information used in experimental design. Perhaps, in other words, a degree of bias against 'received opinion' was involved in the long gap between fundamental observation and mechanistic understanding.

Suggesting that scientists, being no different from nonscientists, could harbor bias might elicit little argument today. Even the idea of scientific progress as 'linear' might be considered by many more an ideal rather than reality. This certainly is the view of some philosophers of science, such as Thomas Kuhn (*The Structure of Scientific Revolutions*), who have speculated that so-called 'paradigm shifts' permeate scientific discovery. Such shifts are said to explain why scientific progress can seem more like stop-and-start movement rather than smooth passage. Integral to such nonlinear progress, so it is said, is bias both for and against new explanations of data.

Of course, all sciences have worked through paradigm shifts on what their data mean; this is as true in immunology as in other disciplines. One classical example in immunology was the postulation, over 40 years ago, of two types of lymphocytes, B and T cells, which was vigorously opposed at first. Another involved the tangled history of 'suppressor networks', which were hotly debated over two decades ago as central regulators of immune responses. Probably both new thinking and molecular approaches eventually confirmed B and T cells but consigned suppressor networks to the waste bin. For both as well, bias in favor and against the hypotheses certainly was involved—in the former, by opposing what was in fact true, and in the latter, holding onto what in fact was explanatorily empty.

What will tomorrow's immunology be like? Will the 'innate' and 'adaptive' immune system distinction remain a useful dichotomy? Will technologies such as microRNA and two-photon imaging revolutionize our understanding of immune regulation? It is impossible to know. Beyond factors scientists cannot easily influence, such as the pace of technological progress, it is worth emphasizing one important element that scientists do have control over: the potential for bias to a degree that holds back progress. Perhaps such bias is unavoidable in how science actually progresses. Some would agree. However, is it too naive to hope, on the thirty-fifth anniversary of the paper by Kleinschmidt and colleagues, that three decades between seminal observation and molecular understanding is the exception and not the rule? We certainly hope it is.