Nobel Ideals & Noble Errors

Great scientists don't make mistakes, do they?

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Christian Eijkman shared a 1929 Nobel Prize "for his discovery of the antineuritic vitamin." His extensive studies on chickens and prison inmates on the island of Java in the 1890s helped establish a white rice diet as a cause of beriberi, and the rice coating as a remedy. Eijkman reported that he had traced a bacterial disease, its toxin and its antitoxin. Beriberi, however, is a nutrient deficiency. Eijkman was wrong. Ironically, Eijkman even rejected the current notion when it was first introduced in 1910 (Allchin, 1996; Carpenter, 2000). Although he earned a Nobel Prize for his important contribution on the role of diet, Eijkman's original conclusion about the bacterium was just plain mistaken.

Eijkman's error may seem amusing, puzzling, or even downright disturbing — an exception to conventional expectations. Isn't the scientific method, properly applied, supposed to protect science from error? And who can better exemplify science than Nobel Prize winners? If not, how can we trust science? — And who else is to serve as role models for students and aspiring scientists?

Eijkman's case, however, is not unusual. Nobel scientists have frequently erred (Darden, 1998). Here I profile a handful of such cases. Among them is one striking pair, Peter Mitchell and Paul Boyer, who advocated alternative theories of energetics in the cell. Each used his perspective to understand and correct an error of the other! Ultimately, all these cases offer an occasion to reconsider another sacred bovine — that science is (or should be) free of error, and that the measure of a good scientist is how closely he/she meets that ideal.

An Error for Every Nobel?

Consider first Linus Pauling, the master protein chemist (Nye, 2007; Magner, 2002, pp. 357-359). Applying his intimate knowledge of bond angles, he deciphered the alpha-helix structure of proteins in 1950, which earned him a Nobel Prize in 1954. He also reasoned fruitfully about sickle cell hemoglobin, leading to molecular understanding of its altered protein structure. Yet Pauling (1970) also believed that megadoses of vitamin C could cure the common cold. Evidence continues to indicate otherwise, although Pauling's legacy still seems to shape popular beliefs (Hurd, 2007). His unqualified advocacy eventually led to him losing sources of financial support. Pauling sometimes described the source of good ideas as having lots of ideas, and throwing away the bad ones. That may well characterize science. Yet it highlights the question of how one recognizes bad ideas and how long they may linger, with what effect, before being thrown away.

Pauling's ideas about vitamin C partly echoed another Nobel Prize winner, whom he called "the most charming scientist in the world": Albert Szent-Györgyi (Allchin, 2007). Szent-Györgyi isolated vitamin C and helped identify it as ascorbic acid. Later, he buoyed research by showing how vast quantities of it could be extracted cheaply from the paprika peppers of his native Hungary. He also claimed, erroneously, that vitamin C participates as an intermediate in mitochondrial reactions and that it could cure various medical conditions. Szent-Györgyi received a Nobel in 1937 "for his discoveries concerning the biological combustion processes." He had helped resolve a debate about those reactions — showing how oxidations leading to proton transfers could be reconciled with electron flow and the use of oxygen. He also helped elucidate the role of fumaric acid (although he identified it incorrectly as a catalyst, rather than an intermediate). Szent-Györgyi went on to contribute to muscle physiology, demonstrating the role of ATP in actin and myosin interaction. Yet he also promoted many spurious claims, such as having discovered yet another vitamin (vitamin P), and treating diabetes with succinic acid and cancer with ultrasound or mushroom juice! For every fruitful idea Szent-Györgyi offered, it seems, there was at least another that was equally mistaken. Given his heroic renown, of course, the errors often remain in shadow.

The 1908 Nobel Prize in Physiology or Medicine marked a pair of discoveries — and perhaps a pair of errors. Paul Ehrlich had characterized the immune reactions of agglutination, bacteriolysis (via complement) and hemolysis. His work embodied the then-popular approach to immunity, which focused on blood chemistry. (The very first Nobel, only seven years earlier, had been to Emil von Behring "for his work on serum therapy" — with its hope for curing all infectious disease through transfusions of blood sera.) Ehrlich, however, also denigrated cell-oriented approaches as utterly misguided. He erroneously excluded any role for phagocytes, say, or for immune action mediated by what we now know as T-cells. Such processes had already been observed and investigated by Ilya (Elie) Metchnikov — who shared the 1908 Nobel with Ehrlich. Metchnikov, in his turn, erred in dismissing the promise of the humoral approach. The Prize Committee recognized the complementary contributions

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together, signaling that they regarded the respective claims of limited scope as unfounded (Bibel, 1988; Silverstein, 1989; Magner, 2002, pp.278-285).

Another striking error belongs to Alexander Fleming, who shared a 1945 Nobel Prize for the "discovery of penicillin and its curative effect in various infectious diseases." In a story widely retold, in 1928 Fleming noted the antibiotic properties of the fungus *Penicillium* in a discarded bacterial culture. Yet after further investigations, Fleming considered the substance useful only as a topical antiseptic, at best. It did not have profound therapeutic potential, he concluded. Still, Fleming found it useful in controlling bacterial growth that would otherwise contaminate vaccine production, one of his duties at St. Mary's Hospital. Years later, Ernst Chain and Howard Florey (who would ultimately share the Nobel Prize) published their first studies about penicillin's efficacy. Fleming continued to remain relatively aloof until the first successful of clinical trials (Macfarlane, 1985, pp. 177-180, 187-189). Ironically, Fleming failed initially to recognize the potent "curative effect" that has since made his own modest discovery famous and, in a sense, exceptionally meritorious.

What of the famed co-creators of the DNA model, James Watson and Francis Crick? (Surely *they* did not err?) Having established the structure of DNA in 1953, they went on to probe the relationship between DNA and proteins and to interpret its "genetic code." In 1958 Crick proposed a theoretical guidepost: "Once information had passed into protein it cannot get out again." This "central dogma" became expressed in Watson's 1965 book, *Molecular Biology of the Gene*, as:

Watson's simple formula gradually eclipsed Crick's and gained widespread currency as expressing a family of truths beyond doubt. First, the cellular functions of information (inheritance) and enzymatic catalysis (metabolism) were differentiated into distinct molecular types. Second, only DNA could self-replicate. Third, information flowed irreversibly from DNA nucleotide sequences through RNA to amino acid sequences. All three principles later yielded to exceptions – although not without controversy. Indeed, it is a measure of the depth of this suite of errors that each counter-discovery itself earned Nobel recognition. The Foundation honored Howard Temin and David Baltimore in 1975 for discovering reverse transcriptase – which produces DNA from RNA; Sidney Altman and Thomas Cech in 1989 for discovering ribozymes – RNA that can fold on itself and catalyze certain reactions; and Stanley Pruisner in 1997 for characterizing prions – proteins that can "reproduce" (or at least provide the "information" to transform similar proteins into new, disease-causing agents). (The 2006 prize announcement for Andrew Fire and Craig Mello implied that RNA interference, too, violated the central dogma – by interrupting the "normal" transfer of information from RNA to protein – URL: nobelprize.org/nobel_prizes/medicine/laureates/2006/illpres/2_central_dogma.html). All these discoveries indicated that the "dogma" of the "central dogma" was ill-conceived.

Francis Crick, for his part, never advocated all the wrong ideas implied by Watson's expression. Crick himself was not completely free of error, however. He seems to have not understood fully the meaning of the word "dogma." He chose it when he meant something very different (an unjustified belief, rather than an inviolable tenet) (Judson, 1979, p. 337). Crick tried to clarify his meaning in 1970, but the very label continued to signify to others that they should regard the central dogma erroneously as – well, dogma.

Crick earns note for yet another, more substantive error. He became increasingly impressed by the complexity of the cell's protein-making process. He could not imagine the circumstance under which it could have originated here on Earth. Thus, in 1981 he endorsed the notion of panspermia – that life originated elsewhere and arrived here by deliberate (though unspecified) means. Quite understandably, scientists did not receive this "maverick" idea with the same esteem and respect as the double helix model.

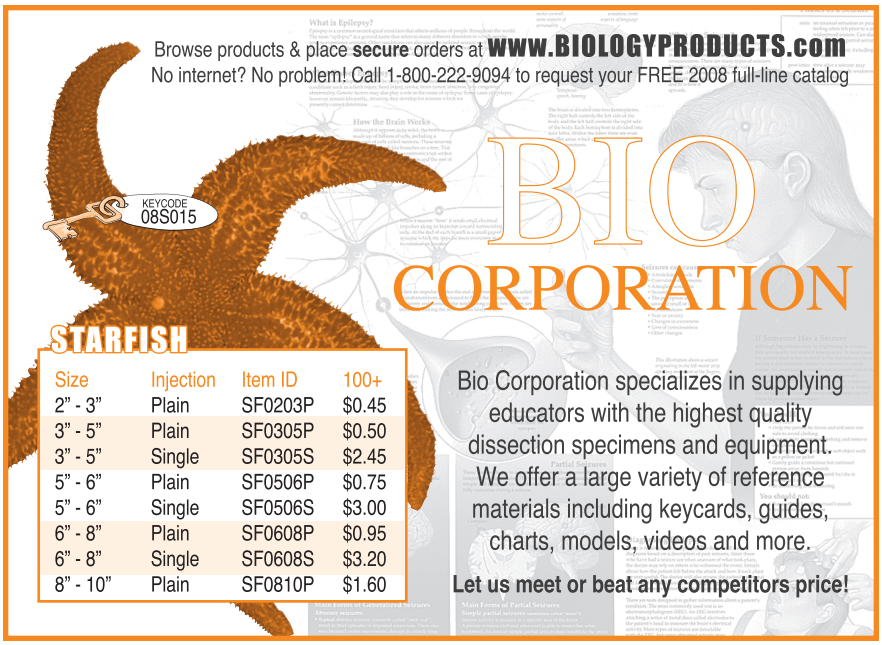
Finally, consider John Eccles, recognized in 1963 for discoveries related to the "ionic mechanisms ... of the nerve cell membrane." More specifically, Eccles helped characterize the transmission between neurons. At some synapses, he found, an impulse hyperpolarizes the post-synaptic membrane, thereby making it more difficult to trigger a successive impulse. At other synapses, by contrast, the impulse lowers the membrane potential. When the potential is lowered sufficiently (to some threshold) from multiple impulses or synapses, the next neuron starts its own impulse. That also indicated that synapses function chemically. Since nerves can only fire or not fire, the chemical mechanism for combining excitatory and inhibitory signals is critical to producing nuanced and complex responses. Eccles thereby helped elucidate the biological basis of mind (Shepherd, 2007). Yet Eccles also wrote extensively that mind and body were distinct. Ultimately, he argued that the existence of a divinely created soul was grounded in science. While one might localize the phenomenon of consciousness, he contended, there were still liaisons with another (non-material) entity to be described. For Eccles, biology could not explain free will. He could not reconcile strict determinism with the concept of moral responsibility (1952, pp. 271-286). Eccles applied his dualist view to the evolution of the brain, asserting that "there can be no physicalist explanation of this mysterious emergence of consciousness and self-consciousness in a hitherto mindless world" (1989, pp. xiii, 236-245). Today, one can only wonder at how Eccles tried to deploy naturalistic science to non-naturalistic ends, ironically in his own field of expertise, neurophysiology.

Exchanging Errors?

Scientists, it seems, do not always recognize their own errors. That task seems to fall to other scientists. One can thus imagine a circumstance where two scientists could possibly "return the favor" by correcting each other's mistakes. One such case seems to have occurred in cellular bioenergetics over several decades late last century (Allchin, 2002; Prebble & Weber, 2003).

The first error was made by Paul Boyer in 1963. (Fret not! He would earn a Nobel 34 years later.) In the 1950s biochemists were looking for a set of high-energy molecules that transferred energy from the electron transport chain to ATP. After a decade of failed claims from several labs, Boyer reported evidence in the prestigious journal *Science* that he had isolated the intermediate and identified it as phosphohistidine. Relief cascaded through the community. The high profile triumph was short-lived, however. Boyer's lab soon attributed the results to other energy reactions in the cell. (The data were "real," but when proper controls were added, dramatically reinterpreted.) "I was wrong," Boyer later put it bluntly.

Boyer was actually wrong on two levels at once. Phosphohistidine was not the intermediate. Boyer admitted as much. But the very concept of the intermediates, for which everyone had been searching so earnestly, was also mistaken.



Boyer soon reached that conclusion, as well. (If he hadn't found the intermediate using his methods, he boldly speculated, no one would.) Boyer hypothesized instead that the energy must be transferred through energized changes in protein conformation (like a pair of interacting molecular springs). This concept, too, would eventually prove mistaken.

Here, the unexpected solution was introduced by Peter Mitchell. Mitchell was guided in his thinking by a novel principle of vectorial chemistry – that enzymatic reactions happened spatially, for example with reactants and products on different sides of a membrane. Synthesizing many clues, Mitchell conceptualized the intermediate energy state as a proton gradient across the mitochondrial membrane – a chemiosmotic potential. That revolutionary idea ultimately earned Mitchell a Nobel Prize in 1978.

Mitchell's own claims, however, were hardly free from error. In the first formulation of the theory, for example, the chemiosmotic gradient was incorrectly reversed! Mitchell also specified one proton everywhere two were needed. Such "minor" errors were soon remedied. But the unrealistic quantitative analysis had already convinced many chemists that Mitchell's notions were fundamentally flawed.

Most dramatically, Mitchell had a vision about how ATP was synthesized from the proton gradient. Using his foundational principle of vectorial chemistry, he insisted that protons flowed in to the interior of the ATP enzyme and there participated directly in forming the phosphate bond of ATP. That creative concept never fit comfortably with the data. Here, it was Boyer's concept, rather, that prevailed. Boyer had adapted his ideas on conformational change. He reasoned how ATP formed on the surface of the enzyme, and was then released through an energy-requiring change in the enzyme's shape. The energy was provided remotely by protons rotating the enzyme as they re-crossed the membrane to lower energy levels. Those insights were recognized in a 1997 Nobel Prize. Ultimately, Boyer and Mitchell had both been right (partly). –And both had been wrong (partly). Their perspectives neatly complemented each other's blind spots.

Role Models & Real Models

Well, what is one to make of all this error among the world's most highly regarded scientists? Do these examples make science entirely meaningless? Hardly. We cannot discount the great discoveries. Nor their great discoverers. Indeed, the errors seem informative just because the scientific credentials of those who made them are unassailable.

Ultimately, if Nobel Prize winners can be mistaken, then any scientist can be. Science is a human endeavor. And no human is perfect. "To err is science," we might say.

Still, healthy science can root out error. As the cases of Boyer and Mitchell (or Ehrlich and Metchnikov) exemplify, contrasting views cross-check each other. They promote completeness of evidence. The chief safeguard against persisting error, then, seems to be not blind skepticism, but actively engaged diversity. Science is empirical, but it is also, ideally, social (Longino, 1990; Solomon, 2001).

What does all this portend for the classroom, where Nobel Prize winners are typically celebrated as role models? Historian Stephen Brush (1974) once wondered if less-than-ideal portrayals of scientists shouldn't be restricted to "mature audiences" only. "Should the history of science be rated 'X'?," he asked (alluding to the then-new film rating system).

Brush was ambivalent. The heroic image, he suggested, might contribute to recruiting future scientists. On the other hand, the human dimension seemed valuable for non-scientists in understanding the nature of science. The dilemma has renewed vigor now, with explicit mandates to teach "the history and nature of science" and "science as a human endeavor" (BSCS, 1993; NRC, 1995; Allchin, 2004). Do we portray real scientists, mistakes and all, or more inspirational but fictional ideals?

Questions of honesty and integrity aside, such a choice, I contend, reflects a false assumption. Why suppose that role models should be flawless? Why expect that great individuals, like those profiled above, never make mistakes? Why is making errors not noble? The errors that should concern us are not those of the scientists themselves, but our wildly-idealized yet widely-held expectations of them.

Role models need to be realistic. Indeed, I suspect that human-scale role models – "real models" – will bring more esteem to science and generate less disillusionment than scientific fairy tales. We owe our students plentiful inspiration, sustained encouragement, and well informed guidance, not phantom goals.

An understanding of science is incomplete without acknowledging that scientists – even Nobel Prize winners – can err. We may equally want to highlight that such errors are generally found and remedied through the social structure of science. Teachers, too, may find in that lesson a healthy reminder. Science education aims not just to nurture prospective Nobel laureates, but also to build a diverse, balanced scientific community.

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