Comment

Transformation

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Well, this year's Nobel Prizes have been announced and once again no monthly columnist was awarded the Prize in Literature. I put this down to a long-standing and unreasonable prejudice in favor of serious writers. The science prizes were, as they often are, somewhat controversial, not because the winners didn't deserve to win - I certainly think they all did - but because there are others who seem to be equally deserving, and who therefore perhaps should have shared the awards. In general, I think the various Nobel Committees do a pretty good job of selecting worthy recipients, but often err on the side of too few awardees for any given discovery or advance. To be sure, it's hard to get it right, especially with the limit, set by Nobel's will, of three winners per prize, but given the collaborative - and competitive - style of modern science, one or even two winners would seem to be too few most of the time.

The disappointment for those who might have - or should have - been included must be acute. Awarding a prize in a given field often means no more prizes will be given in that area. If one's whole career has been devoted to winning a Nobel, the sense of injustice, perhaps of failure, could be overwhelming. But it needn't be. It wasn't for the man who did the greatest experiment in the history of biology with his own hands, and never won the Nobel Prize, even though he lived on for more than half a century after the experiment changed biology forever. His name was Maclyn McCarty, and he was the junior member of the team of Avery, MacLeod and McCarty that proved that genes are molecules of DNA.

I only knew Mac, as everybody called him, for the last few years of his life (he died 2 January 2005 at 93 years of age). He was one of the happiest people I ever met, and also one of the nicest. (The two often seem to go hand-in-hand - perhaps if we are to be nice to others, we must first be nice to ourselves.) In any case, Mac McCarty was totally comfortable with who he was. He never volunteered to talk about the extraordinary work that he had been a part of, back in the 1940s - he was far too modest a man to do that - but he could be cajoled into it, and I never tired of sitting with him, listening to his marvelous anecdotes about that exciting time.

In 1928, Frederick Griffith, an English army doctor, wanted to make a vaccine against a *Streptococcus pneumoniae*, which caused bacterial pneumonia. Though he failed in making the vaccine, he stumbled on a demonstration of the transmission of genetic information by a substance that was to be called the "transforming principle". He found that the bacterium had two forms when grown on agar plates, a smooth (S) and a rough (R) form (see Figure 1). The R bacteria were harmless, but the S bacteria were lethal when injected into mice. Heat-killed S cells were also harmless, but when live R cells were mixed with killed S cells and injected into mice, the mice died, and the bacteria re-isolated from those mice had been 'transformed' into the S type. This experiment strongly implied that genetic material had been transferred from the dead to the live bacterial cells. It was hard to be certain of this, or to know exactly what genetic material was transferred and was responsible for the transformation process, but a small number of scientists eventually realized that in understanding this experiment lay the key to understanding the molecular basis of heredity.

At Rockefeller University in the mid 1930s, Oswald T. Avery and Colin MacLeod carried out a more elegant experiment: they showed that simply putting dead, lethal encapsulated S pneumococcus Type III in a Petri dish with a live, unencapsulated and harmless R strain would cause the live strain to become virulent. They then began to isolate the substance responsible for transferring virulence. In 1940, McCarty - who had just finished his residency in pediatrics at Johns Hopkins - joined Avery's lab and also began working on the problem. By this time Avery's team was already homing in on DNA as the most likely transforming principle. Mac's special skill as a biochemist was not only useful in preparing highly purified DNA; it also led him to

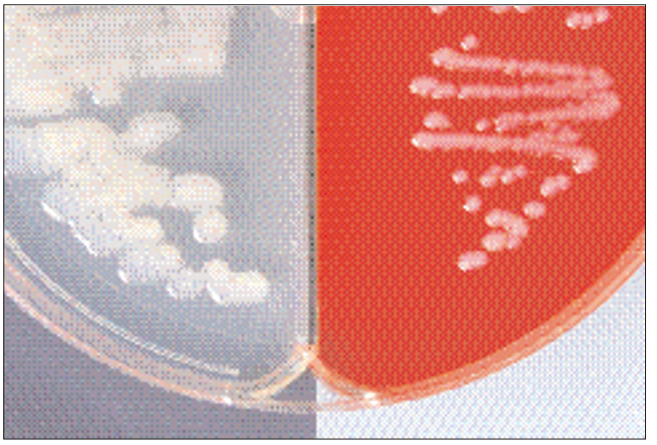

Figure 1
Rough and smooth bacteria. Rough colonies on blood agar (right) and smooth colonies on bicarbonate agar (left) of cultured *Bacillus anthracis*. Picture CDC/Dr. James Feeley.

carry out the definitive control experiments, which showed that the transforming principle was destroyed by the enzyme DNase but was untouched by proteases, glycosidases, or enzymes that digested RNA. In 1944, Avery, MacLeod and McCarty published, in the *Journal of Experimental Medicine*, the paper on transformation that transformed biology forever. It showed - conclusively to anyone with the wit to see it - that DNA was the genetic material.

Despite the powerful evidence in the paper, this conclusion was not accepted by many influential scientists. Chief among these was Avery's Rockefeller colleague Alfred Mirsky, a biochemist, who lobbied for years to deny Avery and his team the recognition their work deserved. Mirsky was convinced that proteins had to comprise the genetic material and believed Avery's DNA samples had to be contaminated with them. He seems to have persuaded the Nobel Committee, because although Avery and his associates were nominated repeatedly in the years following their discovery, they never won the Nobel Prize. Avery died in 1955, age 76 (which, by the way, means he was 65 when he published the discovery of the century - that's for those of you who think that older biologists are over the hill). The assertion that he didn't live long enough for his work to be appreciated is nonsense: by 1952 it was generally accepted that genes were composed of DNA and that the Avery paper was the work that had proven it. (To be fair, Avery himself did not help matters. He had a quiet and self-effacing personality, presented his work in a low key manner, and was averse to any sort of speculation. His presentations were few, and when invited to speak at international meetings he usually sent his younger collaborators.)

Nobel Prizes may not be awarded posthumously, so that was it for Avery, but Mac McCarty lived another 50 years after Avery's death; the Committee had ample time to rectify their mistake in his case. They never did. MacLeod harbored some bitterness over that slight, but Mac didn't seem to. He was modest, happy, spoke well of others, and generally seemed to be having a very good time nearly all the time. If you met him, you would never have known that he might have suffered the greatest injustice in the history of biology.

People often make themselves miserable chasing recognition. When they don't get it, they often become bitter; when they do get it, they sometimes become either insufferable because they have it or depressed because it doesn't really nourish them the way they'd hoped. Mac never got the recognition he deserved: he, Avery and McCloud should have won a Nobel Prize, and it's to the everlasting shame of the prize-givers that they didn't. I know of scientists who have brooded over lesser slights the way Gollum brooded over the loss of the One Ring. If Mac ever did, he never showed it. Here's what he said about Mirsky in his book, *'The Transforming Principle: Discovering That Genes Are Made of DNA'* (New York: WW Norton & Co.; 1985):

> "As far as I was concerned, I was in the position of being on the same faculty with Mirsky for the remainder of his life, and it made no sense to continue to behave as though we did not know each other. In the end, we arrived at a congenial relationship, even though one could hardly say that we were close friends."

It may have seemed sensible to Mac to be cordial to Mirsky, but I wonder how many of the rest of us could have done it.

The good news is that he did eventually get a lot of attention, especially toward the end of his life, when his importance to history as the only survivor of that period was appreciated. After all, he had carried out, with his own hands, the greatest experiment ever done in biology. I know of scientists who have thought of themselves as minor deities because they had done something far less important. Mac never seemed to think of himself as anything but an ordinary human being. One of my graduate students went to New York once to be interviewed for the Helen Hay Whitney postdoctoral fellowship competition. He came back to my lab and told me that his interviewer was a very pleasant elderly scientist and that they had spent a delightful couple of hours together. I asked who he was, and he said, "McCarty, I think - he told me to call him Mac." I asked if he knew who he had just been talking to. He had no idea. I wonder how many other people could have sat for two hours with a young scientist and never bothered to tell them that they were in the presence of one of the men who had proven that genes were made of DNA.

That was the great irony of Mac McCarty's life and career. He found the universal principle of transformation, and yet he himself was not transformed in any way by the discovery.

He carried out the greatest experiment in biology, yet he never acted like someone who had done anything very special. I don't know if you could say that he discovered the secret of life - Watson and Crick laid claim, with some justification and their customary sense of self-importance, to that title - but I do think he might have discovered one secret of a happy life.

Wouldn't it be great if there was some way to rectify injustices like the one that he and his colleagues suffered? I think there is. It may be impossible to award Nobel Prizes posthumously, but there is no provision in Alfred Nobel's will that would prohibit the various Nobel Committees from recognizing neglected scientists in some other fashion. I propose that, every year, at the same time the Nobel Prizes are given out, the Committees designate scientists as 'Nobel Committee Honorees'. The only requirements for such distinction are that the scientists in question be deceased and that their work be of seminal importance and not previously awarded a Nobel Prize. There's no Hall of Fame for science, and it's probably just as well that there isn't (I'm not a fan of places of pilgrimage), but the Nobel Foundation has a pretty terrific web site (http://www.nobelprize.org) where these scientists could receive a little of the honor that was their due. Having the Nobel cachet attached to it will give it the stature they are entitled to. I'm not in favor of limiting the number of honorees in any year, but if there must be a limit it should be set high, like at least five.

Such a simple gesture might do a little to ease some of the hurt that comes along every October. Unlike some people, I'm not a believer in abolishing awards like the Nobels; I think our profession is too little recognized in general, and the huge publicity these prizes engender is good for all of us. But I do think there's a lot of unfairness, unintentional for the most part, that goes along with the Nobel Prizes, and my suggestion may help remedy that. At the very least, someone who missed out in a year when their field was recognized could cling to the hope that some day they might still receive something of their due.

So here are my nominations for the 2007 Nobel Honorees. In Chemistry, I suggest Josiah Willard Gibbs and Ludwig Boltzmann for their pioneering contributions to the theory of chemical thermodynamics. In Physics, I would propose Lise Meitner, J Robert Oppenheimer and Leo Szilard for their seminal contributions to the harnessing of atomic energy. And finally, for their landmark discoveries on the nature of the genetic material, I nominate, for the 2007 Nobel Honors in Medicine or Physiology, Rosalind Franklin, Oswald Avery, Colin MacLeod, and Maclyn McCarty.