Book review

Rank, reinvention and the Nobel Prize

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Experiment Eleven
Peter Pringle
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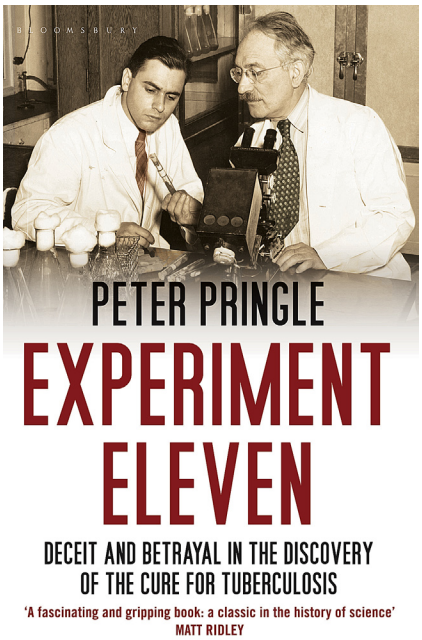
A scientist's first commandment: *"thou shalt not take credit for thy junior collaborators' work"*
— Max Perutz [1]

The story of streptomycin is no ordinary tale. On August 23rd, 1943, in an isolated basement room, a brave and determined graduate student, Albert Schatz, began his quest to cure tuberculosis. He, with his soil bacteria and virulent tubercle bacilli, was banished to that room by his supervisor Selman Waksman, who, like everyone else, dreaded the infection. Waksman never visited Schatz's workroom. Schatz's moment of discovery of an effective antibiotic was a key step in developing a treatment for tuberculosis; in the longer term streptomycin had to be combined with other drugs, but the antibiotic saved the lives and spared the suffering of millions. Streptomycin meant the end of innumerable sanatoria, institutions funded by misplaced hope and peopled by the forlorn [2]. Peter Pringle's excellent book *Experiment Eleven* details how a simple discovery dominated and remodelled the lives of both these two scientists. It tells of a bitter legal fight over credit and a misallocated Nobel Prize. And, like the best of dramas, it reaches outwards, to illuminate scientific behaviour at the time, and forwards, to change our perceptions of scientific ethics today.

Pringle has spent three years excavating clues from many sources, both personal and public; his search was helped by Milton Wainwright, who first reported extensively on the injustice done to Schatz [3]. Now Pringle, with the help of archivists at Rutgers University Libraries, especially Erika Gorder, has found Schatz's lost labnotes. He also mines records from the Mayo Clinic and from Merck and details the machinations of the public relations department at Rutgers as well as its legal representatives. With the willing help of Schatz's wife Vivian and other living witnesses Pringle has dug up dirt and written a devastating account. It is remarkable that Waksman alone received the 1952 Nobel Prize for physiology or medicine: it was given for "*his discovery of streptomycin, the first antibiotic effective against tuberculosis*" [4] and perhaps not so remarkable that subsequently "Schatz's contribution was soon forgotten" [1].

Schatz was 22 when he was drafted from Waksman's lab in 1942 and sent to the Army Air Forces hospital at Miami. He saw the effects of infection on the wounded and although penicillin had just become available, it did not work against Gram-negative bacteria, such as those causing typhoid and cholera, or against *Mycobacterium tuberculosis* (TB). Schatz felt powerless as he spent his free time comforting the dying. When he returned to Waksman's lab in the summer of 1943 he began a personal mission to find a new and wide spectrum antibiotic. In August he undertook 'experiment eleven' where he tried a different method of sampling and found a promising effect of the soil bacterium *Actinomyces griseus*, some of which came from a swab of a chicken's throat given to him by another student, Doris Jones. In October, an extract was tested in chicken eggs and found to kill typhoid bacteria without harming the eggs (previous antibiotic candidates isolated in Waksman's lab had proved highly toxic).

Then Schatz wanted to test the new antibiotic against pathogenic TB bacteria. Waksman acquired some of these bacteria and Schatz personally worked out how to isolate enough of the new chemical and did the bacteriological tests. He worked day and night, often snatching sleep on the floor of the lab. Overdoing it, Schatz became ill and collapsed with pneumonia: "Waksman was the only member of the staff who didn't visit him"* in hospital. But streptomycin inactivated the bacteria and Schatz was so elated he sealed up some test



tubes and gave them to his mother as a memento! Schatz then isolated enough streptomycin for trials by William Feldman and Corwin Hinshaw at the Mayo clinic; they tried the antibiotic on guinea pigs infected with TB. Streptomycin was not toxic and the guinea pigs were cured. Tests on humans soon followed; the first life to be saved was that of a two-week-old baby in September 1944.

Pringle then tells us the history of the commercialisation of streptomycin; it had many twists and turns. But the public story of the discovery was subject to continuous modification as Waksman rewrote history. Don't get me wrong, I believe Waksman deserved credit; it was his lab and by following the lead from Russian researchers, he had doggedly searched for antibiotics produced by soil microbes long before Schatz arrived, he organised the collaboration with the Mayo clinic, he set up the commercialisation with Merck, he did the politics. However, the moment of discovery belonged to Schatz: he put his life on the line, he did the research, he discovered and then purified the antibiotic and did the first crucial tests.

Waksman's subsequent campaign is meticulously detailed in Pringle's book and Waksman's misappropriation emerges step by step with painful clarity. Pringle describes how the self-serving combination of Waksman himself

*Quotations shown unattributed in the text are from *Experiment Eleven.*

and the public relations department at Rutgers together undertook an ultimately successful siege on the Nobel Prize. They invented a "parable", a fraudulent myth about a robotic and nameless assistant who followed orders from the top but contributed no more to the discovery than the chicken from which the bacteria were isolated. They misinformed gullible commentators, they took advantage of the tendency of journalists to simplify and to lionise, they twisted the truth, they rubbished the facts, they hid the money-trail, they covered up the original patent (which belonged to both Schatz and Waksman), it goes on and on.

I read Pringle's well-documented account open-mouthed as I witnessed Schatz's reputation and his brave contribution being obliterated. Waksman must have been conscious of what he was doing, he avoided mentioning Schatz on every occasion, including his first public lecture on streptomycin, at the Mayo Clinic in 1944. In that talk he relied on using the royal "we", and mentioned no collaborators at all, even Feldman and Hinshaw, who were in the audience! He painted a meretricious picture of himself as an idealistic hero who gave any money away. But actually he had been secretly receiving royalties from Merck, some $350,000 dollars (1940s!) without telling Schatz. Perhaps feeling some guilt, he offered Schatz small sweeteners of three $500 dollar cheques but he did not tell Schatz where the money came from. Schatz assumed they were personal gifts from Waksman and at first refused to accept.

No surprise then that Schatz was outraged when he later found out that Waksman had been double-crossing him. Schatz was so upset he went to the law to reclaim his status as a joint discoverer. The legal arguments are beautifully spelt out by Pringle: because the investigation uncovered so many inconsistencies and untruths in Waksman's reinvention of the past, the lawyers for Rutgers got cold feet and they settled: Schatz was legally recognised as a co-discoverer of streptomycin on December 30th 1950.

In 1950, Waksman went travelling on an extensive campaign for the Nobel Prize in Europe, while the image-building publicity continued in the press at home. *The American Magazine* titled their puff: "He turned his back on a million dollars: An intimate glimpse of a distinguished scientist who passed up a sure fortune for the greater reward of freeing mankind from disease" [5]. Schatz was not mentioned. So it was that the Nobel was awarded in 1952 to Waksman alone. Feldman was surprised and wondered in a letter if the prize had been awarded to Waksman for a "long professional career pertaining to the microbiological investigation of the soil from which streptomycin finally emerged". But that was not the justification given nor could it have been because of Alfred Nobel's will — Nobel Prizes then and now are given for a specific discovery, not for a laudable career and not for courtly behaviour!

In my opinion, streptomycin was Schatz's discovery and Waksman's lab and infrastructure made it possible (as did the chicken one could add, but that "counterparable" would also be very unfair). After the announcement, Waksman and supporters attempted to influence the Nobel Assembly to change their justification for the prize and indeed at the ceremony in Stockholm there was a shift to recognise the "parable" that Waksman had originally invented, and also a hint that the prize was for a long effort. This reinvention was eagerly underwritten by Waksman in his acceptance lecture when he managed to avoid mentioning Schatz at all; although there was an appendix where Schatz was listed along with others, half of whom "had not even been at Rutgers when Schatz had discovered streptomycin". "This is how Waksman wanted the world to see Albert Schatz".

Indeed, this was largely how the world subsequently saw Schatz, and also as a litigious student who acted above his station in suing his supervisor; "many of Waksman's contemporaries took his side without apparently acquainting themselves with the details of the case"[3]. Schatz had trouble finding employment and his discovery was not properly recognised for the rest of his career, until long after Waksmans death in 1973 when, in 1994, Rutgers awarded Schatz their most prestigious medal.

So with hindsight, who should have received the 1952 Nobel Prize? It becomes clear from this book and from Max Perutz's account that the prize might in justice have gone to Schatz, Waksman and Jorgen Lehmann for two separate discoveries. Lehmann used brilliant logic to invent PAS, a drug that, in combination with streptomycin, cured patients with TB. Stockholm's records show that Lehmann and Waksman were nominated in 1951 and 1952, and Schatz in 1952 for the prize. In general there are criticisms one can make of the decisions of the Nobel committee at the Karolinska Institutet; for example, one could say that a discovery they choose to honour is not the right one; but I think that kind of criticism is inappropriate; it is for them not us to make that selection, there are so many valuable advances in science to choose between. But to fix on a specific discovery and then not to recognise the real discoverer(s), that I think should be open to question. Pringle's book makes it clear why the Karolinska were misled and I have also seen the opinion of Einar Hammersten, the main advisor to the committee in 1951/2. His opinion was weakened by a lack of knowledge of how the work was done and by a questionable tendency to include the rank of each candidate as a factor in his considerations.

There may be an endemic injustice in the choice of Nobel laureates and other awardees: that senior scientists — and it is they who nominate, are consulted and decide — tend to overlook junior candidates. Apart from the Schatz case, it happened with the omission of the student Charles Best from the 1922 prize for insulin, an error which was acknowledged 50 years later by the Nobel Foundation [6]. It may have happened with Jocelyn Bell Burnell, who was also a student when she found pulsars with her supervisor Anthony Hewish. And it appears to have happened this year in respect of part of the 2011 physiology or medicine Nobel Prize. The prize concerns innate immunity, a field that began with Hans Boman and colleagues in Sweden, who studied how insects protect themselves against bacteria and fungi. For this year's Nobel Prize, credit was given particularly for a paper in 1996 on *Drosophila* genetics; it presented clear evidence that the Toll pathway

is instrumental against infection. The prize was given to the lab chief, Jules Hoffmann. But the first author on the paper, Bruno Lemaitre, has argued that he initiated the project and planned it, that he made the discovery that mutations in the Toll pathway rendered a fly impotent against infection, that he wrote up the first version of the paper and that Hoffmann's scientific contribution to the discovery itself was largely limited to improving the paper's style [7]. And the facts asserted by Lemaitre are not disputed. It is documented that Hoffmann never properly acknowledged Lemaitre's contribution to the Toll discovery. Jeremy Garwood has researched the matter and alleges that Hoffmann also manipulated perceptions, just as Waksman had done half a century before, by writing numerous reviews, giving many lectures, making copious use of the royal "we" and by networking to raise his own profile at the expense of his junior collaborators [8].

Why worry about who receives Nobel Prizes? I think we should because the prizes act so powerfully to define what we value in science; the prizes create role models whom scientists try to emulate, they draw attention to the greatest discoveries and announce who is responsible for them. The choices of particular laureates often receive worldwide approbation but, whether they do or do not, they should be open to scrutiny. For in Nobel's will his express intention was clear: "the most worthy shall receive the prize" [6].

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Q & A

Eric Davidson

Eric Davidson graduated from the University of Pennsylvania in 1954 and received his PhD from Rockefeller University in 1963. He remained at Rockefeller until 1971 when he moved to Caltech in Pasadena, California. He was elected to the U.S. National Academy of Sciences in 1985, and is at present Norman Chandler Professor of Cell Biology in the Division of Biology, Caltech. He is the author of 5 books and over 400 papers on developmental gene regulation and evolution of genomic programs for development. For the last decade his work has focused on theory and operation of developmental gene regulatory networks.

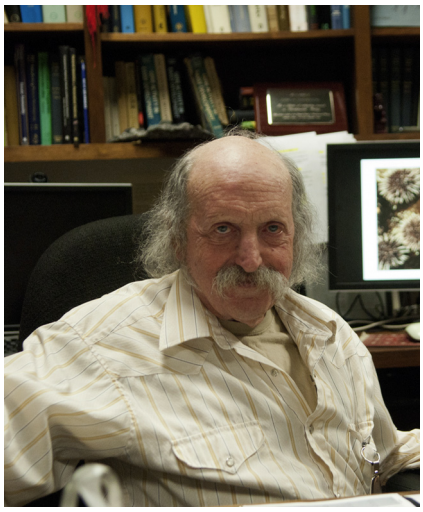

Photo: Lance Hayashida.

What specific events in your early life most strongly affected your path into a career in biology? All developmental processes occur stepwise, and so did my own trajectory. Though from my earliest recollections I was always interested in science, I went to typically unedifying, casually violent and prejudiced provincial 1940s–early 1950s American public schools, from which only a tiny fraction of male students ever went to college, and where there were no particular scientific opportunities available. But the day I walked into 10th grade biology class, I saw an elderly and kindly, intelligent-looking teacher in a long severe dress and heavy black shoes. She was Miss Krum. A fateful idea popped into my mind: I offered to her to make all the class lab preps for the year, if I would be excused from weekly quizzes. She looked at me over the tops of her old fashioned thick glasses, and said "Do you know how to make microscope preps, young man? "Yes Ma'am" said I, and went home and fixed up some stained onion skin and a few paramecia etc. on a microscope a family friend had given me one Christmas; and that was it: by the end of that year, and the weekly experience of looking long and hard at some new preparation of fascinating cells or eggs, or studying ancient teaching sections, I was hooked for life. And so that summer I went to Provincetown, Massachussetts as always, for that was the location of the art school of my father, Morris Davidson, who was then a famous painter. He made an arrangement with one of his art students that by another serendipity a week later had landed me in a wonderful laboratory at the Woods Hole Marine Biology Laboratory (MBL), just at the other end of Cape Cod. The student was Ellen Donovan, the wife of Prof. L.V. Heilbrunn and an artist in her own right. L.V. was an MBL scientific institution. I was to wash dishes in his lab, and to make my keep, at night collect whatever biological wastes each lab had put outside its door, ground up horse meat, empty clam shells, dead sea urchins, whatever. But when I walked in the door, 'Boss', as L.V. was universally known, growled at me "You are going to do research if you are going to be in my lab!" He gave me a problem, and a clue to the possible answer, and the rest is history. It was 1953, and my first publication describing the successful conclusion of that summer's work was in the 1954 Biological Bulletin Abstracts of the previous summer's research proceedings. In August, I had had the terrifying experience of presenting this work in the big auditorium before the whole MBL Corporation. But on the strength of that project I later that year became a Westinghouse Science Talent Search Winner, and on the strength of that I got to go to the University of