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Carl Woese in Schenectady
The forgotten years

Larry Gold

University of Colorado and SomaLogic; Boulder, CO USA

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Many of the authors of these short pieces (who were invited to contribute by Robin Gutell) have already written or spoken about Carl Woese since he died at the end of December 2012. My own thoughts were published in PNAS on February 26, 2013. Still saddened by Carl's death, I re-read what I wrote at that moment. The article was OK, although it was not strong enough for what Carl taught us: he deserved better. I'd like us to admire what Carl did over 50 years (which is a given), and to admire even more the way he did it. While Carl's accomplishments were huge, his intense dedication to the ideas that consumed him was even more impressive.

Carl's educational history is well known. He went to Deerfield Academy, then to Amherst to get an undergraduate degree with a major in math and physics in 1950, and then on to Yale, getting a PhD in biophysics under Dr Ernest Pollard in 1953—a short time for a PhD thesis, even back then. Carl's thesis was entitled "Inactivation of Animal Viruses by Physical Agents," with those agents, including heat and ionizing radiation, being relevant to a story I will share below. Carl next tried medical school at the University of Rochester for a couple of years (1953–1955) and then returned to Yale to be a Research Associate from 1955 until 1960.

What Carl did next is not well known, except as an event in his CV. I had a unique window into that excursion by the young Carl, having received a gift in the summers of 1961 and 1962: I worked in Schenectady, NY (my home town) at the General Electric Research Labs, the place that Carl went for his first job after his Research Associate position at Yale. Carl was hired to be the first biophysicist at GE, joining a group that had no clear idea why GE ought to care about the work they would do. Over the more than 50 years that I worshipped Carl, he never shared one word about why he took the job in Schenectady. Would he have told me that those brief 3+ years were the forgotten ones? Perhaps not—perhaps Carl's time in Schenectady prepared him for the extraordinary career that followed. In fact, that is my hypothesis.

And so began my experience with the irresistible Carl, who took me on. In those two summers in Schenectady he taught me (and those around him who watched) how he decided what science to do. Beyond his discoveries, Carl's most important legacy might be the way he answered that question. All scientists choose (or ought to choose) what they do carefully—one spends years, often, following those passions, and those moments of choice are the start of a long investment. Witness if you will what "happened" to me after Craig Tuerk did his first SELEX experiment—it has now been nearly 24 years since November 1989, and I still think of almost nothing else!

Carl had no interest in the biophysics equipment he bought for his new lab at GE; he was primarily interested in talking to people, and there were not many people then at GE with whom to talk (a situation that has changed dramatically—GE has filled the Schenectady lab with wonderful people). Carl was exploring what he wanted to do with his scientific life, having decided against becoming a physician. Carl was doing what everyone ought to do, i.e., looking into what he really thought. Carl's brain, quite openly and generously displayed for all, was a thing to behold, and it remained on display for a half century.

A Story

I was given a remarkable task in the second summer at GE: I was going to "cure cancer" by doing an experiment on rats. All of what follows is from memory, since among the many things I did poorly was keep good notes. Dr Charles Huggins from the University of Chicago had been able to generate mammary cancers in female Sprague-Dawley rats with 100% incidence after a single dose of 20 mg of 7, 12-dimethylbenzanthracene (7, 12-DMBA) dissolved in sesame oil, given by a stomach tube. Several breast tumors were palpable in each rat within 50 days of a single administration. Our boss at GE, Dr Hans Rozendaal, told me to do that experiment (that is, to repeat what Huggins had done) and also to attempt to prevent the animals from getting mammary cancers by heat-treating the breast tissue of half of the animals. Dr Rozendaal promptly went sailing in Scandinavia for the summer, or so I remember, leaving the inmates in charge of the lab. By the end of the summer I would be (with Carl's help) a famous cancer researcher, like Dr Huggins, but I would have the added pleasure of blocking the growth of the 7, 12-DMBA-induced tumors. To my astonishment, Carl offered to help me do the work. Remember, I was a kid, and Carl was thinking about his next area of inquiry. But he offered, and I accepted with delight. I ordered 80 or so female Sprague-Dawley rats of

Correspondence to: Larry Gold; Email: lgold@somalogic.com
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the right age, found a place to house them (Union College had an animal facility), made up some DMBA in sesame oil (as per the Huggins protocol), and spent a day—with Carl—giving 20 mg to the 80 rats through a stomach tube. Tragically, about 20 of the rats got DMBA in their lungs, and promptly died—this was one of the awful lessons of that summer. Carl just peered at me wisely, and did not offer to take over the procedure—he would have also been inept. We now had about 60 rats that were going to get breast cancer within two months, and we were going to prevent 30 of them from getting cancer by treating their breast tissue with heat. Carl and I began planning exactly what heat treatment protocol we would try.

Neither Carl nor I had any good ideas—maybe little heating pads might have done the trick for those 30 rats in the experimental group. Finally, we had the thought that we would use a water bath, set to 45 °C, and that we could place the rats into that water bath and let them swim around for the period we would choose (several times a day, we thought), thus exposing their breast tissue to elevated temperature (as an aside, I often wondered over the years what we would have invented had Huggins induced tumors of the back—would we have taught those poor rats to do the backstroke at 45 °C). We realized right away that a simple water bath would not do, because the rats were strong enough and annoyed enough to climb out, so we rigged a sink to be at around 45 °C and further rigged a screen to place over the swimming rats, perhaps a few inches above the water level, so they could not escape. By the end of the summer the 30 treated rats had been reduced to about five (the others had drowned), and they were examined carefully for signs of breast cancer—not a single one of the survivors had a palpable breast tumor, which was stunning. Less stunning was the fact that of the 30 rats who had been spared the sink but who had received their 20 mg of 7, 12-DMBA, not one had breast cancer either.

We had failed to repeat the work of Huggins, a body of work repeated by many people in the 40 years since the original publications. In fact, when Dr Huggins won the Nobel Prize in Medicine in 1966, he said during his acceptance speech "Whereas a single feeding of a solution of 7, 12-DMBA always (my emphasis) induces breast tumors…" we might have said "wait a minute, what about the unpublished work of Gold and Woese?" Fortunately, we realized that we were not gifted experimental scientists and that we just had been kind of dumb. Interestingly, the idea that had stimulated Dr Rozendaal at GE is still on people's minds. A quick look at the literature (through Google) identifies many papers in which DMBA-induced rat mammary cancers are treated with heat, although no paper I have found uses the simple elegance of a 45 °C swimming pool! In addition, Carl's PhD studies were aimed at heat inactivation of viruses—to a math and physics guy like Carl, tumors and viruses might have felt similarly organic.

To be fair, I have just outed one of the true heroes in my life. As confessionals go, outing a friend and mentor when he cannot defend himself is just wrong; however, the statute of limitations has long passed. Carl and I never handled a lab animal again, as far as I know, and for sure we realized that scientists have an obligation to the better treatment of laboratory animals on which one works.

The Quirky Carl Woese—A Hypothesis

Why did Carl offer to help me, and what was on his mind? Why did Carl waste his time with me? He had a new job, he had to do something with biophysics at GE, and what he really did during those years was figure out the rest of his life. He and I spoke often about the way he saw the coding problem; that is, he spoke and I listened. I did not care—or understand—why he wondered about the chemical/evolutionary relationships between codons and the amino acids they specified—Carl might have been a rabbi explaining some preposterous story from the Old Testament. For people who knew Carl in the later years, after he became famous, he always seemed a bit mystical and charming. His passion for big truths about big questions was allowed to mature in Schenectady, and I got to watch that process unfold for two summers, and for much longer—that piece of him never changed.

The papers that he wrote while he was at GE have been mostly forgotten. After he left GE to go to Urbana, he focused for a very long time—more than a decade—on more thoughts about coding. These were serious efforts to understand the translational apparatus (including 5S RNA, which he hoped would be a sufficient molecule to understand what he needed to understand about evolution), and then, finally, his breakthrough paper in 1977 (with George Fox) that forever made Carl into the "three kingdom" guy when he finally wrote that rRNA was the molecule that carried our evolutionary history.

There is a science trajectory that we can see in hindsight—from wondering about coding to understanding that coding was about the translational apparatus, and that the translational apparatus carried the key to the evolution of the protein world. Carl was the earliest proponent of what we now call the "RNA World Hypothesis"—he reached that conclusion from logic alone—one could not simultaneously evolve proteins and RNAs, and the heart of the breakout from chemistry into biology was the translational apparatus itself. Carl did not need the discovery of catalytic RNAs to believe in them as a logical necessity.

When I knew him early, I was dumbfounded by his passion. As I knew him and his entire body of work later, I was more than dumbfounded—amazed is closer to the truth—by Carl's ability to create in his brain, alone as far as I can tell, the idea that rRNA is both the metric for evolutionary histories and the primitive molecule at the center of the breakout to Darwinian evolution. Carl considered evolution after that moment to be nearly automatic; interesting in detail, but not surprising. His focus for most of the past 30 years was on that moment prior to what we all call Darwinian evolution (even though Carl spent a lot of time explaining how unfair to Alfred Russel Wallace that word choice is; Carl really didn't like Darwin for being, he thought, a "science thug" and perhaps even a science thief).

And so, by the end of those forgotten years, Carl's passion was set on the pursuit of the molecules that were required for chemical evolution to transition to biology. Carl knew that those molecules were the rRNAs. As his career progressed, Carl focused more intently on understanding the moments prior to speciation, a moment that Carl believed involved large amounts of Lateral Gene Transfer prior to the time that cell membranes became less permeable. Carl stood not on the shoulders of anyone else, but on his own; Carl created the idea that rRNAs were the remnants and drivers of our evolutionary path.

A Conclusion

For 50 years I hung on to my old friendship with Carl, often by only a thread: I would see him every few years, and we would email. Over the five years before he died, and well before he was diagnosed, I started to see him more frequently. Carl even made a trip to Boulder to let us honor him for a few hours and have dinner with him. Because of my interests in translation and RNA, I knew all the (at one time) young people that Carl collected—Robin Gutell, Harry Noller, Norm Pace, Gary Olson, Mike Yarus, and others, and I knew many people in Urbana who remain friends: Gene Robinson, Debra Piper, Harris Lewin, and in particular, Nigel Goldenfeld, the physicist who was the last of the lucky people to be mentored and befriended by Carl (and with whom Carl published fascinating and revealing papers that will take us years to fully understand). The parallel life that Carl led—along side of the extraordinary science he did—was one of friendship and mentorship. Carl was only interested in doing science that mattered, and that was a large piece of his mentoring.

Students and postdocs and even the better assistant professors often wonder, as Carl did in Schenectady, about their life's work—"what in the world should I pipette?" That most difficult question is answered most of the time by careerist choices—"what do others want, what will get funded, can I win the race to publish over others, and so on?" Carl was fascinated by those questions, and yet he refused to be influenced by those concerns. I often tell people, or at least the few who ask me as I recede slowly into the haze, that each day one ought to look in the mirror (while brushing your teeth, for example) and ask if on the way to work you were killed by a bus would anything change for the science you have chosen. If the answer is NO one ought to get back in bed with a good book, walk the dog, or play basketball—one ought to not study the things that have become small scientific cottage industries. For example, I loved alanine scanning the first time I read about it, and didn't love it the next 300 times. Or promoter "bashing"—we do need to use the technologies that evolve in the same way that Carl used Sanger RNA sequencing and then NGS, but always for the purpose of asking and answering a real question. And that was the heart of Carl, the lesson for us all: ask real questions (in your science and in everything else), don't piddle around with the one life you get, even mishandle a few rats with your lucky young friend in Schenectady while you are thinking about the questions that you must study to be alive.

My last visit to see Carl, a month or so before he died, was chilling, and I am still chilled by it at this moment. Carl was tired, he knew things were going downhill quickly, and yet he seemed happy that I was in his living room with his wife Gay. All of a sudden he said something like "I want to give you something" and he walked up the stairs to his study. He rummaged around for a while and then slowly walked down the stairs, carrying two books. The first was his own book from 1967—"The Genetic Code: The Molecular Basis of Genetic Expression"—in its Portuguese translation. Carl said "Here, give this to your daughter Emily. It is so wonderful that she loves languages—this will give her the excuse to learn another." As I said above, "mystical and charming" were some of Carl's qualities. The second book was also for many months a mysterious gift—Carl gave me his copy of "Adventures of a Mathematician" by S.M. Ulam, who had been on the faculty in Colorado, but whom I had never met. I read the book in the evenings, kind of surprised that Carl wanted me to do that. After several sittings, I saw the faintest of pencil marks in the margins—sometimes the equivalent of a yellow highlight, sometimes a question mark, but always faint—Carl was communicating with Ulam, and I was handed an incomplete transcript. One sentence from Ulam's book seemed important to Carl because it was both highlighted and had a question mark—"I am struck by the 'reasonableness' of the arrangements on which life has been shown to be based. The discoveries of the way living matter replicates, everything that followed from Crick's and Watson's models, the nature of the biological code show a sort of comprehensible and almost nineteenth-century type of mechanical arrangements which do not require basic physics for the understanding of how they operate." There sat Carl, the math and physics guy, reading an autobiography by a man he respected, wondering not how biology works today but how it came to be in that pre-speciation moment, amazed I think that Ulam had bought into the last paragraph of Watson and Crick's Nature paper that famously started "It has not escaped our attention…" and then laid out the next 50 years of molecular biology without wondering, with Carl, how this reasonable thing evolved. Carl gave me that book, I hope, so that I would help keep Carl's torch burning, along with others whom Carl taught, by not forgetting that the moment all living things received the same ribosomes and the same genetic code is worth further consideration.

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No potential conflicts of interest were disclosed.