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MINIREVIEW

Howard Berg's Random Walk through Biology

Michael D. Manson[a]

[a]Department of Biology, Texas A&M University, College Station, Texas, USA

ABSTRACT This minireview presents the career of biophysicist Howard Berg from his first interest in bacterial chemotaxis and motility through the present. After a summary of some of his early work, a series of reminiscences of students, postdocs, colleagues, and family members is presented. In sum, these recollections capture the effect that Howard's scientific life has had on the field of bacterial chemotaxis and motility and on the careers and lives of those who have interacted with him.

KEYWORDS Howard Berg, bacterial chemotaxis, bacterial motility

THE BEGINNING

The years 1972 through 1974 were historic and disturbing. Watergate dominated the news, and prospects in Vietnam looked bleak. But momentous things were being discovered, things on a scale far smaller than we experience with our senses. There were lives whose description awaited someone who could bring physics to bear on biological problems.

Physicists made important contributions to molecular biology before 1972. Understanding the structure of DNA and proteins, the randomness of mutation, and the dogma of DNA→RNA→protein was made possible by the insights of physicists. But physics had made little contribution to understanding of the behavior of whole organisms. Howard Berg changed all that.

The stage was set by Julius Adler. After reading old German literature translated by his wife's mother, he started studying a behavior of bacteria, chemotaxis. Bacteria swim toward things they like, attractants, and away from things they do not, repellents. Adler discovered something surprising. Bacteria respond to attractants and repellents not because they are good or bad for them. They respond to specific molecules, and those molecules neither have to be metabolized nor have to be taken up. They are sensed by receptors on the cell surface, and they can be detected before they enter the cell (1).

This discovery caught the attention of insightful scientists, including Howard Berg (Fig. 1), who was in the process of moving from Harvard to the Department of Molecular, Cellular, and Developmental Biology founded by Keith Porter at the University of Colorado (UC). In transit, Howard stopped at Adler's lab at the University of Wisconsin during the late summer and early fall of 1970.

Jerry Hazelbauer was a grad student with Julius. He and others in the lab thought their group was the only one interested in the molecular basis of bacterial behavior. Howard's visit was the first indication that they would soon be joined by labs around the world.

Before departing Harvard, Howard built a microscope that traced the paths of swimming bacteria. In Madison, he tapped Adler's expertise to establish his own research on bacterial motility. Howard knew nothing about bacteria, so he sought practical knowledge of how to manipulate them. The greatest source of such knowledge in the Adler lab was a long-time research associate, Marge Dahl. Howard spent much time with Marge, and the two of them became good friends. Everyone recognized Howard's academic intelligence; his focus on learning from Marge showed he had practical intelligence.

Howard's presence expanded the horizons of the Adler lab. Jerry found having

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Address correspondence to mike@bio.tamu.edu.

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FIG 1 Howard Berg as he likes to see himself.

someone from "outside" interested in their work was a treat. Howard introduced the lab to unfamiliar ways of thinking about what they were investigating. They had been thinking biology; he thought physics. The lab learned as much from Howard as he did from them. His explanations of physical principles, and his patience with those not fluent in mathematics, foreshadowed his future role for the entire field of bacterial chemotaxis and motility.

Howard was convinced that bacterial chemotaxis could be approached by someone with a Ph.D. in experimental physics, which he had from his work with Nobel Physics Laureate Norman Ramsey. Howard loved the idea that this work had been anticipated centuries previously by Antonie van Leeuwenhoek. Howard purchased a replica of the original microscope (Fig. 2A). He also viewed van Leeuwenhoek's letters to the Royal Society. He best remembers letter 18, which describes the swimming of Leeuwenhoek's "little eels" (*Spirillum volutans*).

One thing Howard discovered was suggested by a simple observation. Two bacteria whose flagella are held together by antibodies counterrotate, a motion no beating flagellum can generate. Also, antibodies binding to the flagellar bundle of *Escherichia coli* block motility, an effect that can be explained by rotating flagella but not beating ones. The case for flagellar rotation was laid out in a 1973 paper by Berg and Anderson

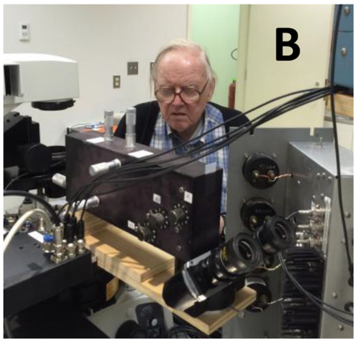

FIG 2 (A) Howard casts a critical eye on a replica of the van Leeuwenhoek microscope. "Running and tumbling, little motor spins around. Howard sees them swim!" (Ariane Briegel wrote the haiku and provided the photo, which was taken by Eliza Wolfson [reproduced with permission].) (B) Howard with a slightly more complicated microscope. (Photo courtesy of Linda Turner, reproduced with permission.)

(2). The clearest demonstration took the form of tethered cells (3); cells attached to a glass surface by a single flagellum rotate and alternate between clockwise (CW) and counterclockwise (CCW) rotation. Attractants promote CCW flagellar rotation, and repellents promote CW rotation.

Flagellar rotation provided an explanation for a behavior Howard demonstrated in a sophisticated way. His tracking microscope mapped the course of swimming bacteria (4). Harvard physicist Paul Horowitz, of SETI (Search for Extraterrestrial Intelligence) fame, helped with the electronics and data analysis. Bacteria run and tumble; long straight swims (runs) are punctuated by very abrupt changes in direction (tumbles). The result is a three-dimensional random walk, like diffusion. CCW flagellar rotation produces runs; CW flagellar rotation causes tumbles.

Work from two labs showed how this behavior enables chemotaxis: Dan Koshland's, with Bob Macnab, at UC Berkeley (5), and Howard's (6). Using different methods, they reached the same conclusion. Bacteria sense and respond to spatial gradients by biasing their random walk in the favorable direction. They run longer up an attractant gradient or down a repellent gradient. They measure chemoeffector concentration as they swim, comparing the instantaneous concentration with the one a few seconds earlier. If an attractant increases or a repellent decreases, the cell suppresses tumbles and continues running. Howard thus characterized bacteria as optimists. This mechanism requires that bacteria have a short-term memory to compare concentrations (7). This memory, called adaptation in the context of chemotaxis, consists of covalent methylation and demethylation of the receptors (8), which occur on a slightly longer (seconds as opposed to milliseconds) timescale than chemoeffector binding and release. Methylation resets receptor activity after increased attractant occupancy or decreased repellent occupancy, and demethylation resets receptor activity after decreased attractant occupancy or increased repellent occupancy. Bacterial chemotaxis soon became the behavior best known at the molecular level.

The rationale for using rotating helical flagella for propulsion, and for using temporal comparison for sensing gradients, is beautifully explained in the essay "Life at Low Reynolds Number" by Ed Purcell (9). Bacteria in water are like humans in molasses. Viscosity means everything, inertia nothing. Only the activity of the instant matters. There is no gliding. Nor does a bacterium gain more nutrients just by swimming or by stirring the medium. Diffusion is fast enough to bring nutrients to a stationary cell. Even if a bacterium swims in a favorable direction, it cannot do so for long because Brownian motion changes its trajectory. Periodic tumbles are necessary to allow the cell to resume the correct course. Chemotaxis brings cells to regions where the attractant concentration is higher or the repellent concentration is lower.

Howard's mentoring and his style of doing science have inspired the people who have worked with him. The remainder of this minireview features reminiscences of people whose careers and lives were changed by Howard Berg. I begin with students, move to postdocs, and end with colleagues and family.

STUDENTS

Steve Block (Ph.D. student at UC Boulder, 1974 to 1979; Ph.D. student and postdoc at Caltech, 1980 to 1984) spent a gap year, after getting an undergraduate degree in physics at Oxford, working with Max Delbrück at Caltech. Steve washed dishes, prepared media, and conducted research on light adaptation in *Phycomyces*. Steve was studying grad school options when one day Max summoned Steve to his office. He declared, in his German accent, "Steve, I have decided! You go to Colorado." Why Colorado? "I want you to work for Howard Berg." That was that. Max loved Howard's work. In 1974, Steve moved to Boulder for what was, in effect, an arranged scientific marriage.

Steve played the banjo. Summers, he left Boulder to travel to bluegrass festivals throughout the West. This lifestyle did little to advance his scientific career. By 1979, Howard's patience ran out, and he wrote Steve a brief note reminding him that unless he could focus on research, he would never amount to much in science. Steve resolved to do better and was perhaps saved by the fact that, in January 1980, the Berg lab relocated to the sober sanctuary of Caltech, where Howard was recruited as a successor to Max Delbrück. Steve's productivity improved correspondingly, although he snuck off occasionally to the Banjo Café in Santa Monica, where he met his future wife, Kathleen.

Looking back, Steve credits three events for establishing his career in science. The first was when Max Delbrück took Steve under his wing and introduced him to biophysics. The second happened in 1975, when Max sent Steve to work for Howard Berg. Steve feels that Max kindled a small flame that Howard turned into a burning torch. Howard taught by example, not by lesson. But there were lessons to be learned, provided one paid attention. The third was that Howard taught Steve how to think critically and encouraged him to work with his hands as well as his head. Howard was the living embodiment of "a biophysicist is a biologist who builds his own apparatus." Howard opened Steve's eyes to the power of live demonstrations in teaching. He embodied the words of Ed Purcell, "Physics is where you find it." And Howard taught Steve, as he taught many, how to write a scientific paper and to deeply appreciate the power of a well-crafted phrase. But no prose resonates with Steve quite so much as the short note he got in Boulder, when Howard reminded him that success flows from identifying the right balance of priorities and then applying oneself appropriately.

Chris Kaiser (UC Boulder, 1976 to 1977; Caltech, 1980 to 1981) remembers his father, Dale, a renowned microbiologist, returning from UC Boulder and describing a scientist who built a microscope to track swimming bacteria. Chris read some papers and was immediately hooked. This was what he had been looking for—a complex behavior controlled by a binary switch in the rotational direction of a molecular motor. The opportunity to work with the scientist/inventor who built this instrument was a call that Chris could not resist. Chris thanks Howard for taking him seriously, despite his youth, and welcoming him to a world of creativity, rigor, and the belief that every feature of the natural world, no matter how subtle, can be measured. Chris remembers Howard, eyes wide, body gyrating, arms waving wildly, explaining how the flagellar bundle flies apart during a tumble.

Howard loved scavenging parts and tinkering in the shop, but with something important, like the tracking microscope, things got serious and he proceeded with the care of a master machinist. The machine shop at Boulder had two rooms—one for everyone and another with precision tools that were only for Howard and the fastidious departmental machinist. Chris never saw Howard at work in that inner sanctum, but he recalls Howard's pride in facilitating acquisition of a Hardinge lathe that was "so quiet it could run in your living room."

Howard was creative both in coming up with new ideas and ways to test them and in devising controls based on physics. Howard explained that the original experiments using rapid mixing to show that bacteria respond to temporal gradients of attractants (5) contained a logical flaw in fluid dynamics. There was a brief period during mixing in which steep spatial gradients existed, to which the bacteria might respond. Howard eliminated this possibility by producing a purely temporal gradient by generating an attractant molecule using an enzyme.

Even in hindsight, the outlook of the lab in Boulder feels fresh and exciting to Chris. The first known rotary motor in biology could be studied in great detail by watching spinning bacterial cells tethered to a cover slip by a flagellum. Chris does not think anyone, even Howard, foresaw the true power of these studies. The flagellar motor comes already attached to a visible "bead," the bacterial cell body. The experiments tracking those spinning cells were precursors to the single-molecule studies that have since revealed the mechanisms of other biological motors, including the rotating F_oF_1 ATPase and the motors that move along linear cytoskeletal or nucleic acid tracks.

Jeff Segall (Ph.D. student at Caltech, 1980 to 1984) found the Berg lab at Caltech a remarkable experience. The lab motto was "turn obsession into excellence." While looking for a lab in graduate school, Jeff was attracted by the challenge of understanding the rotary motor. He joined the Berg group to learn how the motor works. At the time, Howard was looking for steps in the rotary motion. He and Paul Horowitz had designed a machine that could follow motor rotation to detect subtle fluctuations that would reflect those elusive steps. The real-time rotation of a tethered bacterium was visualized for the experimenter by oscillation of needles of moving-coil meters reflecting the *x* and *y* orientations. Paul compromised his esthetic standards to accept the use of what he considered ugly meters, forever burdening the rotation detector with the name "ugly meter box." It failed to detect steps, but Howard did not despair. The ugly meter box could follow the direction of rotation with high time resolution, and Howard convinced Jeff to use it to determine the time it takes for bacteria to respond to a chemotaxis stimulus. The ugly box was successfully repurposed, and other students and postdocs found ways to use it to study different aspects of chemotaxis.

Jeff thinks that ingenuity and opportunism are the hallmarks of Howard's approach to science. This flexibility helped students navigate the frustrations sure to be part of science. Steering Jeff away from the rotary motor to examine the kinetics of the chemotaxis response led to successes that have kept Jeff inspired ever since and have given him confidence to tackle difficult problems in areas far removed from bacterial chemotaxis.

Markus Meister (Ph.D. student at Caltech, 1981 to 1987) attended Howard's memorable 1980 Caltech physics seminar. With inspired practical demonstrations, some unplanned, Howard convinced everyone that bacteria rotate their flagella, whereas similar-looking motions by flagella and cilia in eukaryotic cells are merely waving, not rotating. Markus was drifting, looking for an interesting research project, and Howard agreed to take him on for a summer. His supervisor was Howard's son Henry, then 12 years old. The goal was to find steps in the rotary motor by analyzing videos using a cutting-edge Apple IIe computer. They made good progress together, and Markus was rewarded by being encouraged to come up with a dissertation project of his own.

Markus recalls that Howard taught him everything about being a scientist. Howard had a knack for designing a decisive experiment to distinguish two alternative explanations. He also encouraged people to think hard about experiments that had already been done. In fact, his splash into the field of bacterial motility—the 1973 paper claiming that flagella rotate—was based exclusively on prior reports available to everyone. The only figure in the paper is a hand-drawn sketch. Markus suspects that the resistance Howard encountered from the scientific establishment was based on chagrin at their failure to interpret facts there for everyone to see.

Markus calls Howard's style of scientific writing "minimal description length." Every sentence, every word, must be justified. Markus experienced this with his paper about measuring proton current through the flagellar motor (10). Howard's happiest moments were when he rearranged sentences so that an entire paragraph could be dropped. He was less subtle reviewing a draft of Markus's dissertation; multiple pages simply disappeared. Markus now recognizes the hygienic value of this style: with fewer words, it is harder to hide shoddy thinking. Howard applied the same principle to scientific figures: every drop of ink needed justification. We do not use ink on vellum anymore, but the same rule applies to pixels.

When Markus joined the Berg lab, Jeff Segall and Steve Block had just measured the biphasic impulse response of the chemosensory system in *E. coli* (11). Bacteria respond with a brief moment of joy to a pulse of a positive stimulus, followed by slightly longer period of disappointment when it is gone. Joy and disappointment are well balanced, and the average happiness is more or less independent of what happens. Markus finds this to be a universal aspect of life at every level of complexity.

POSTDOCS

Ken Foster (postdoc at UC Boulder, 1973 to 1979) was Howard's first postdoc in Boulder. His work with Bob Smyth was not closely related to Howard's, but Howard was always supportive. Howard slipped Ken into a Gordon Conference session just before lunch. Ken showed the quarter-wave-stack antenna underlying the eye spot of *Chlamydomonas* and suggested that the photoreceptor was rhodopsin. After his talk, senior microbial physiologist Wolfgang Haupt declared, "Impossible!" Ed Purcell came to Ken's defense. During the discussion, Ken heard rain pouring. There was a sudden clap of thunder, and the room went dark. Nature had spoken. After lunch, Ken defended his claim to a group convened to attack his idea. Ken turned out to be right.

In 1984, Ken's group at Syracuse, working with Koji Nakanishi, could not convince *Nature* to review their study showing that the phototaxis receptor in *Chlamydomonas* is rhodopsin. Howard persuaded *Nature* to send the manuscript out for review. The article became a cover story (12) and a photo in *Nature's* annual calendar. It is good to have Howard on your side.

I, Mike Manson (postdoc at UC Boulder, 1975 to 1979, and at Caltech, 1980 to 1981), met Howard in Charley Yanofsky's home after a seminar Howard gave at Stanford in 1972 or 1973. After an amazing talk, Howard seemed totally at ease in a crowd of faculty, postdocs, and grad students. Like Chris Kaiser, I was fascinated by behavior. A visit to Howard's lab in Boulder confirmed my choice, as did Howard's 1975 popular treatise in *Scientific American* (13).

I got a National Science Foundation postdoctoral fellowship to study electrical signaling in chemotaxis, based on the idea of bacteria as little nerve cells. Later, while discussing another outlandish idea, Howard imparted this wisdom: "The best hypothesis is not contradicted with facts on hand but can be dismissed with one good experiment." That is the way science should be done.

I arrived in Boulder for the annual Berg family Thanksgiving dinner in 1975. Howard's wife, Mary, a scholar of South American literature, and their three offspring, Henry, Alec, and Elena, became an important part of my life for the next 6 years. Theirs was a welcoming home that later included my wife, Lily, whom I met in Boulder on 4 July 1977. A few photos from our 1979 Boulder wedding bring back pleasant memories (Fig. 3).

Attempts to measure changes in membrane potential during chemotaxis led indirectly to an important discovery: that flagellar rotation is driven by a proton motive force (14). Things worked that way in the Berg lab. Serendipity. Or, fortune favors the prepared mind.

Howard's intellect and knowledge can be overwhelming. In my first weeks in Boulder, I envisioned spending 80 hours a week reading the literature just to be able to converse with Howard. I soon realized that my training as a bacterial geneticist also contributed something new. It took some convincing, though. In response to my desire to isolate mutants, Howard said, in near shock, "Why would you wreck my magnificent machine?"

I recall Howard receiving huge containers of Army surplus equipment and sorting through the jumble with Henry and Alec to find something useful. On weekends, Howard would manufacture things in the departmental machine shop. It was hazardous to speculate about experiments requiring some arcane device. On Monday, that device would be on your bench. Even if rethinking showed that the experiment was doomed, I felt compelled to do it.

Howard takes to heart the maxim that brevity is the soul of wit. Writing a paper with Howard, manuscript drafts would be exchanged. I would add explanations, Howard would abbreviate or delete them, and so on, back and forth. Finally, we would sit down at his home on a Saturday afternoon with a bottle of fine brandy and go over the manuscript, a sentence at a time. By evening, a mellow understanding and a final draft had been reached.

Alan Wolfe (postdoc at Caltech, 1985 to 1988, and at Harvard, 1988 to 1989) trained as a geneticist. A friend brought him the Caltech Annual Report, opened the page to Howard Berg, and said, "That's where you should do your postdoc." Alan wrote to Howard and received an immediate reply, "When can you start?" Then, "Wait, I don't know anything about you. Are you going to the biophysics meeting?" "No, I'm a geneticist." Later, Howard confessed that he needed a geneticist in his lab. Although Sandy Parkinson had been very generous in providing strains, Howard felt it was time that his own lab started generating the ones they needed.

Alan remembers four experiences in the Berg lab. First, every time Alan opened his

FIG 3 Mike and Lily's wedding. (A) Howard at bat in the prenuptial bride versus groom softball game. This game was the inspiration for the Random Walks, the City League softball team that Mike organized many years later in College Station, TX. (B) Steve Block breaks out champagne after regaling the wedding crowd with his banjo. (C) Mary and Elena Berg. (D) Howard and Elena take in the exchange of vows.

mouth, Howard would say, "25 words or less, Alan!" Many years later, acknowledging his selection as Faculty of the Year at Loyola Medical School, Alan remembered that and followed Franklin D. Roosevelt's admonition, "Be brief, be sincere, be seated." To the relief of the audience, Alan's "speech" was 45 seconds long. He was thinking about Howard the whole time.

Second, the folks in the lab at Harvard knew two things about Howard. He always wore a light blue shirt and khaki pants to work, and he was extremely observant. So, for his birthday, they decided to test how observant he was. Everyone in the lab wore Howard's uniform, walking in and out of his office, roaming around the lab, having coffee in the break room, all in Howard's presence. There was no recognition, none at all. At lunchtime, everyone crowded into the conference room. Mary Berg and Ed Purcell arrived, also dressed like Howard, who now noticed and said, "twins." Then he looked around at the rest of the group and said "Ooooh!" It was hilarious.

Third, Alan and Howard were writing a paper when Alan had a pressing personal problem. Alan was clearly distressed and distracted. Howard told him, "Take care of it and then come back." It took 3 days. Nothing more was said. A few months later, Howard let Alan move to Harvard several months before the rest of the lab, again for personal reasons. He also let Alan bring his young children to the lab when they were out of school. Alan feels that Howard helped him to learn how to combine a family life and a career in science.

Fourth, Alan learned from Howard how to focus. Howard would often say, "Not now; I am thinking about X's problem." It might take an hour or a week, but eventually, Howard would be done with X. Now there was time for him to think hard about Alan's problem. Alan learned it was worth the wait.

To summarize, Alan notes that Howard is both smart and wise, with full understanding of the different connotations of those two terms. Alan adds that Howard is also a mensch, the greatest compliment in Yiddish for a person's humanity.

Victor Sourjik (postdoc at Harvard, 1998 to 2003) was impressed by the scientific freedom Howard gave to people in his lab. On Victor's first day, Howard suggested some projects. One was to measure motor rotation using polarization microscopy, and the other was to use fluorescence resonance energy transfer (FRET) to detect CheY-FliM interaction at single motors. Victor never worked on either project; he soon became excited about applying fluorescence microscopy and FRET to analyze chemotaxis signaling pathways. Not only did Howard not mind, but for months he did not even ask about progress. It took Victor a while to get used to having so much freedom.

Victor recalls that his typical approach was to go to Howard with an exciting new result or with enough data to write a paper and not bother him in between. However, whenever anyone wanted to talk, the door to Howard's office was always open. He worked with rewards rather than a whip. An hour after Victor showed Howard his first FRET results, Howard asked Victor whether he objected to a salary raise. Victor's next paycheck was a third higher.

One thing Victor could not do on his own was make hardware changes in the microscopy setup (Fig. 2B). Victor remembers telling Howard that something needed to be changed. The next morning Howard was in the microscopy room taking measurements for his next visit to the machine shop. The only time Victor changed the setup himself was when Howard was on sabbatical in Europe. Victor decided not to tell Howard his plans, as he was afraid Howard would shorten his sabbatical just to come back to work in the machine shop.

Ady Vaknin (postdoc at Harvard, 2002 to 2007) has memories similar to Victor's. What Ady thought Howard enjoyed most was to find a unique solution to a technical problem, preferably over the weekend. Howard's passion showed itself in the small things. Ady recalls that the microscope used for single-cell FRET work was the only one in the world using shotgun pellets. To balance the microscope stage, Howard built a box and filled it with just enough lead shot, bought at a local gun shop.

Ady remembers that Howard once told him, "Doing science is like walking in the woods with a destination in mind, but when you encounter a beautiful flower along the way you should take time to admire it." The FRET work in Howard's lab provided a good example. Ady's original project was to characterize rotation of the C-ring and its interaction with CheY. (The C-ring is the cytoplasmic ring of the flagellum that interacts with the proton-conducting stator units MotA and MotB to generate rotation and to determine CW or CCW rotation.) CheY carries the signal for CW rotation from the receptors to the flagellum. However, Victor Sourjik and Tom Shimizu had recently developed a method for using FRET to analyze chemotaxis signaling (15). Ady adapted their advances to carry out single-cell FRET imaging and fluorescence polarization to detect the physical response of chemoreceptors to stimuli. Howard encouraged this type of cross-fertilization to generate innovations that led to breakthrough discoveries.

Birgit Scharf (postdoc at Harvard, 1994 to 1998), trained as a molecular biologist, has somewhat different memories. She recalls Howard's skepticism with things outside his expertise. For a paper on constitutively active CheY (CheY**), the amount of CheY** made at different levels of IPTG (isopropyl-β-D-thiogalactopyranoside) induction had to be precisely quantified (16). Birgit struggled to get reliable results, as there were obstacles, from sample preparation to blotting to detection. It took months of troubleshooting each step. When Birgit presented all these details, things not normally considered at Berg lab meetings, Howard said, "Well, I will not believe Western blot results in a paper ever again."

Pushkar Lele (postdoc at Harvard, 2010 to 2015) joined Howard's Harvard lab after reading Howard's book *E. coli in Motion* (17). He decided that the way to learn from Howard was to inundate him with questions. Howard had an elephantine memory. He could pluck out any relevant publication from the reprint jungle in his office. Howard responded to Pushkar's naive queries patiently. Pushkar took away the lesson that even the famous can be patient with those they mentor.

Pushkar would follow Howard to the machine shop. Howard would work on the lathe—for hours, sometimes for weeks—to produce complicated microscopic accessories. He called it therapeutic. The machine shop was his motive force. Pushkar learned that pontificating from behind a desk is not as rewarding as hands-on work.

Howard sensed Pushkar's anxiety in working with the legendary ugly meter box. He advised, "Don't be nervous, you're making me nervous," which only made matters worse. One afternoon in the machine shop, Howard plugged in the wrong coordinates for the drill. The piece he had been working was thoroughly ruined, and he uttered a couple of mild expletives. Pushkar remembers chuckling for the entire time Howard reworked the piece. A small, but liberating, moment.

Yilin Wu (postdoc at Harvard, 2009 to 2012) had a Ph.D. in computational biophysics, but, with help from Linda Turner, he became an experimentalist. This was typical in the Berg lab, with colleagues from diverse academic backgrounds, often unrelated to biology, having to learn how to perform experiments.

Almost every weekend, Howard and Mary stayed in an apartment at the Rowland Institute. Yilin used this time to discuss his difficulties and his new results with Howard, who was always happy to help. He would pull out a decades-old paper and point to a specific section. Yilin remembers Howard watching him conduct experiments, smiling, and remarking, "You should document that." Now Yilin is a mentor himself. When his students describe their experiments, he runs to the lab immediately, knowing just how much an encouraging word can help.

Howard had favorite sayings. "If something works, don't reinvent the wheel." "You need to read beyond the abstract." After one seminar, Yilin commented that the work was interesting. Howard replied, "Yes, it is interesting, but not profound." Yilin started to ponder what work was profound. That is, perhaps, something that more scientists should ponder. It is certainly a more compelling question than asking what work is fundable.

Abhishek Shrivastava (postdoc at Harvard, 2013 to 2019) recalls that 3 months after he joined the Berg lab, Howard had bypass surgery. The mood in the lab was somber. Several weeks later, Howard walked into the lab. His surgery, he said, "was a plumbing job. I am as good as new." Over the next 6 years, Abhishek saw Howard push the boundaries of science every day, building a new microscope or fixing an old one. During the lab lunches or hands-on microscope-building exercises, he infected everyone with his passion for science, expanding the love of science by his example.

COLLEAGUES AND FAMILY

Igor Zhulin beautifully captures Howard's ability to inspire awe. Igor gave his first talk at a chemotaxis meeting while he was a researcher in Barry Taylor's lab. Igor was a bit nervous. After finishing and walking back to his seat, he passed Howard. "Not bad" was Howard's laconic comment. Igor remembers it as one of his most cherished compliments.

Rudy Schmitt first met Howard in 1975. As noted previously, Howard had recently shown that bacterial flagella rotate rather than beat, suggesting that there could be a "biological wheel." Rudy accordingly extended his studies on the assembly of the complex flagella in *Rhizobium* to consider behavior. Striking deviations from the *E. coli*

FIG 4 Group photo from the 1990 Regensburg Conference on Signal Transduction. How many of the luminaries can you recognize after 30 years? (Hint: the late and dearly missed Bob Macnab is the one who looks like he is wearing a COVID-19 mask.)

paradigm soon became apparent. While many labs focused on enterobacteria, Rudy, together with Judy Armitage and others, tried to understand "variations on a theme" in alphaproteobacteria. Progress was reported at the 1990 Conference on Signal Transduction in Regensburg (Fig. 4).

In 1995, Howard arranged for Rudy to visit the Rowland Institute, where Howard had unique equipment that could visualize single moving flagella with high-intensity light microscopy. It became clear that the stall of a single flagellar filament in a CW-rotating flagellar bundle changed the swimming direction, as later documented by Birgit Scharf (18). This observation demonstrated that there were ways other than running and tumbling to generate a random walk that could be modified to perform chemotaxis.

Nyles Charon says that having Howard as a collaborator was a godsend. As a graduate student, he had studied the physiology of the spirochete *Leptospira*. He became curious how spirochetes swim; their periplasmic flagella (PFs) are internal. As a new faculty member at West Virginia University, Nyles jumped onto studying spirochete motility; there were few papers on the subject, and Nyles thought he could contribute. Nyles began isolating motility mutants of *Leptospira*. The PFs from these mutants were different. They were straight, unlike those of the wild type, which coil like a spring. A single mutation caused the defective coiling.

In 1976, Howard proposed a model of spirochete motility suggesting that PFs rotate. Thrust is generated by the cell cylinder rotating in one direction and the sheath rolling in the opposite direction. In 1977, Howard visited West Virginia, with the result that he and Nyles collaborated on a model for *Leptospira* motility. The model states that the PFs rotate and that the PFs generate backward-moving waves that propel the cell (19).

Later, Nyles visited Howard's lab at the Rowland Institute and, with Steve Block and Stuart Goldstein, obtained direct evidence that the PFs rotate. Nyles finds work from the Berg lab creative and cutting edge, and he appreciates Howard's broad interest in biology and his honesty, fairness, and willingness to help others.

Linda Turner (UC Boulder, 1974 to 1978; Rowland Institute, 1987 to 2017) loved looking through a microscope as a child but never dreamed of being a scientist until 1974, when she met Howard in Boulder. Howard sat next to her in an electron microscopy class. Linda knew he had built a microscope that tracked bacteria. How did it work? After class Howard took out a mechanical pencil, borrowed a sheet of paper, and captured her imagination with a few lines. He spoke a visual language, one she understood intuitively. Later that year, Linda started working in Howard's lab and learned to use the tracking microscope. Eventually, Howard left on sabbatical, and Linda left to spend time with family. However, they remained in touch and occasionally met.

Years later they got back together at the Rowland Institute. Howard illustrated devices and their use in conversations illustrated with chalkboard drawings. Some were extremely complex and required their partnership to operate: electrorotation and a rebuilt tracker combined with fluorescent imaging, which revealed some amazing images of flagellar filaments on running and tumbling cells (20). Simpler devices were entrusted to her alone. She spent years accumulating data with these devices and creating graphs. Howard's favorite response to the graphs was, "I predicted that." Linda would smile and wonder why she had spent all that time when Howard knew the answer all along. Occasionally, a result would surprise him, and Linda loved such moments. The Rowland lab became her home; life there was filled with fascinating people, especially Howard. It was deeply satisfying.

Elena Berg gives her dad credit for teaching her "how to think." When he helped her with homework, he never provided answers. He pulled out props, drew diagrams on napkins, and made her figure things out for herself. He discouraged rote memorization. Elena sometimes became frustrated by his emphasis on thinking, particularly when she just wanted to be done with her calculus homework. He would remark, "Elena, it's trivial!" Now, Elena realizes that the curiosity and desire to know how things work, inspired by her father, fueled her career as a "soft scientist" (à la her dad) studying animal behavior and evolution. She finds herself channeling her father when she interacts with her students. "In my assignments and exams, I expect my students to explain what they know and to put it into different contexts. They roll their eyes the way I rolled my eyes at my dad, but I'm OK with that."

Elena also feels she learned the importance of scientific integrity from her father. He impressed her with the idea of doing things correctly and not taking shortcuts. If he could do it with a homemade microscope that was "cheaper and better" than what he could buy, all the better. Her dad always shared his ideas with colleagues without feeling that knowledge was his "property." Elena says he knew that the best science will always win in the long run.

Elena has many other memories: her father's "flagellar dances" during his seminars; his teaching props (she recalls a wind-up mouse with rotating arms and red pants); the hours she spent scooting around his Caltech lab on wheeled lab chairs; his lying on the couch at home with his feet propped up, enjoying a chemistry textbook for a little light reading. Those images still make her smile.

Pat Tedesco (UC Boulder, 1973 to 1979), Howard's research technician in Boulder, vividly remembers the flagellar dances 45 years later. Howard's dancing obviously caught the ladies' eyes.

Rasika Harshey gets the last word. She recalls keeping company with Howard at meetings, wanting his insight into the effect of motor reversals on the surface swarming behavior she had discovered in *E. coli*. Her memory emphasizes a different side of Howard than the other recollections. "I think there is only one side to him—gentle and unguarded." That thought no doubt prompted Rasika to write the following limerick for his 70th birthday.

There once was a young prof from Harvard,

Whose thoughts ran ahead light years forward.

They leapt and they danced,

As our science they advanced.

A salute to incomparable Howard!

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