In memoriam

Robert Ader (1932-2011)[1]

I had never heard of Robert Ader until one day in 1974 when he dropped by my office at the University of Rochester Medical Center (URMC). He introduced himself, and told me about his recent taste aversion studies involving the triumvirate of rats, saccharin, and cyclophosphamide. After providing a bit of background, he hit me with his hypothesis (Ader, 1974) that the death of some of the conditioned rats re-exposed to the CS resulted from a conditioned immunosuppression and a consequent failure to effectively eliminate environmental pathogens. We agreed that until this hypothesis of conditioned immunosuppression was tested in deliberately immunized animals, no one

[1] Robert Ader, Ph.D., MD (hc) received his B.S. degree from Tulane University, and his Ph.D. in experimental psychology from Cornell University in 1957. He joined the URMC faculty in 1957 as an instructor and became a Professor of Psychiatry and Psychology in 1968. From 1969 to 1999, Bob held a continuing Research Scientist Award from the National Institute of Mental Health. During 1970-71, Bob was a Visiting Professor at the Rudolf Magnus Institute for Pharmacology in Utrecht, The Netherlands. During the 1992-93 academic year, he was a Fellow at the Center for Advanced Study in the Behavioral Sciences Department at Stanford University. Bob was a past President of the American Psychosomatic Society, the International Society for Developmental Psychobiology, the Academy of Behavioral Medicine Research, and the Psychoneuroimmunology Research Society; some additional accomplishments are mentioned in the main text.

would pay any attention to this novel concept of a reciprocal dialogue between the brain and the immune system. We did the experiment, published the results (Ader and Cohen, 1975) and as they say, the rest is history — a history marked by a paradigm shift and, thanks in large part to Bob's unceasing efforts, the establishment of psychoneuroimmunology as a bonafide interdisciplinary area of investigation.

What history doesn't record is that this and other conditioning experiments marked the start of a 37-year-long friendship as well as an exciting and productive collaboration that changed the trajectory of my life. Apparently I am not alone in this regard. When Bob finally conceded he should retire in July of 2011 from 50 plus years of service at the URMC, Michael Perlis (Bob's former colleague at the URMC; now at the University of Pennsylvania) came up with the idea of preparing a Festschrift in his honor. Jan Moynihan and I solicited congratulatory letters from about 70 of his colleagues in psychoneuroimmunology from all over the world. These "Dear Bob" letters were compiled and privately published (Perlis et al., 2011), and presented to Bob at a small dinner party in his honor. A common denominator of these letters was a reference to the life-changing impact that Bob had on many of the contributors.

> David Eisenberg: *In a lifetime, if one is fortunate, we meet a few individuals who become our lifelong teachers and lifelong inspirations. You are such a person to me, Bob. Nearly three decades ago, you took interest in me and my wide-eyed interests in "alternative" approaches to health care. You challenged me to think rigorously about a range of unstudied questions. You encouraged me, and countless others, to reconsider what we know, or think we know, about the complex relationships between mind and body, volitional choice and conditioned response, genetic predisposition and*

the impact of behavior and the environment on human physiology and the natural course of health and illness. In short, you were and have remained a role model.

Raz Yirmiya: *I still remember vividly my visit to interview with you and the rest of the PNI research community at Rochester in 1988. You and I spent a whole evening and then part of the next day discussing PNI research, including my plans and ideas for the post-doctoral work. I was full of awe and excitement, and had to almost pinch myself to believe that I am talking, one on one, with "the father of PNI". The hospitality, genuine interest, respect, and encouragement that I felt from you, as well as the fascinating and original ideas that you shared with me on that occasion, solidified my decision to enter the PNI area for the rest of my life.*

Cobi Heijnen: *At this moment in my career I realize that our meeting (1986 or 1987) has been the most important push for me to really dive into PNI. You showed genuine scientific curiosity and interest combined with a great intelligence and your typical humoristic approach. In fact "I felt safe" to continue PNI feeling your support. Thank you Bob; I have never regretted it afterwards. I love your genuine interest in people, your warmth, your hospitality, and on top of that your scientific intelligence combined with a far-reaching vision on the field of PNI. Above all, I admire your fighting spirit when you believe in something.*

Mike Irwin: *I had submitted, and you had accepted, two of my manuscripts for the inaugural issue of Brain Behavior and Immunity; these were two of my very first manuscripts as a young Assistant Professor. Your words of encouragement and (did I hear) pleasure in publishing my work placed an "external" value on what I done, which had not yet been articulated by anyone other than collaborators on these projects. This interaction, brief though it may have been, left a lasting impression on me in large part to the high opinion that I had of you and your work in PNI, which I maintain to this day. The friendship you have given so freely to aid the careers of many is a legacy that endures, to be passed to the next generation.*

Alex Kusnecov: *It is not easy to sum up the impact that you have had on my identity as a scientist. It's almost like everything I do has your input still present somewhere hanging over my shoulder. While I still like to think I have developed some unique form of thinking and independence, it would be untrue to say that all*

the checks and balances that I apply to my conceptual and practical designs don't have the Ader equivalent of a "spell check" on my thinking. I think also in some ways, so does the field that you kick-started with your visionary experiments and the 1981 book that all of us still pull off the shelves and admire for its celebration of a fledgling field that was at the time the little engine that could, and magnificently, evolved into the mentors, postdocs, and students that celebrate psychoneuroimmunology in the journal that you started, and in labs throughout the world. What an honor it has been to be your mentee, colleague and friend.

These excerpts show Bob's availability to critically discuss ideas and data and to provide encouragement regardless of the seniority of the investigator or the geographical location of his or her institution—one reason for his profound impact on so many. Another explanation of his impact, I think, is that the sum total of his contributions[2] in the 1970s and 1980s (discussed below) led young and older scientists alike to realize that they were not isolated in their interests, but were, in fact, all participating in an exciting newly emerging (now fully emerged) field called psychoneuroimmunology.

Bob was a brilliant experimentalist who was totally averse to taking shortcuts in designing a protocol. His study designs were elegant in their thoroughness (and mind boggling in the number of animals used). Thanks to all the control groups included in our initial conditioning studies, the papers we wrote were airtight. I remember talking with a well known immunologist colleague and friend who told me that after our paper on conditioned suppression of autoimmunity in NZB/W mice appeared in *Science* (Ader and Cohen, 1982), he and his colleagues devoted a journal club to trying to poke holes in it. When no holes were found, my colleague stopped being a skeptic.

[2] Contributions that included: editor-in-chief of *Brain, Behavior, and Immunity*; initiator and leadership of the PNIRS; senior editor of four ever-expanding editions (1981, 1991, 2001, 2007) of the so-called bible of the field, *Psychoneuroimmunology.*

Although Bob did not teach a lecture course at the URMC, he did teach his postdoctoral trainees (and other scientists, including me) a great deal about the art of experimental design, data analysis, and manuscript writing.

Jon Karp: *I learned more from your Thursday lab meetings than you can imagine. It was not just the science that impacted my life, but the logic and thoroughness of your approach to the scientific process. I carry much of that desire to participate in the best designed experiments as possible with me. I try to teach my students many of the things you taught me about how scientists learn about the world. The details of the science may change, but the definition of what is good science is steadfast.*

Marion Kohut: *Going beyond current thinking, willingness to challenge existing paradigms, believing in your data even when others question your findings, those are the qualities that result in success (at least sometimes!!). Understanding how to set up appropriate controls in experimental design is also essential. I often relay the story about one of my first lab meetings as a postdoc in Rochester with my first exposure to all of the control groups necessary in a conditioning trial (unconditioned stimulus, conditioned stimulus,…. and on and on). I remember thinking, "How many more control groups can Dr. Bob possibly think of?"*

Willem Hendrik Gispen: *Your presence at the Rudolf Magnus Institute in Utrecht, now some forty years ago, had a formidable impact on my development as a neuroscientist. You taught me proper data analysis and scientific reasoning. You gave my mono-world of neurochemistry the multidisciplinary touch that is characteristic of true neuroscience.*

Bob Ader never claimed that our conditioning studies published in the 1970s and 1980s were the first to demonstrate behavioral regulation of immunity. After our first few conditioning studies had been published, Bob learned of some very early papers in Russian that had reported putative conditioned immunological effects. He had these

papers translated and then described and re-evaluated the presented data in a fascinating contribution (Ader, 1981b). Bob also wrote two papers exclusively devoted to the early history of PNI (Ader, 1995, 2000). In these definitive historical accounts, Bob gave full credit to those whose work took place shortly before or around the same time as our 1975 paper. In fact, he emphasized that it was the very juxtaposition of all this information (Bob referred to this as *the right stuff at the right time; Ader, 2000)* that served to substantiate the interconnectedness of behavior, immunity, and the nervous and endocrine systems. That said, why do others join me in thinking of Bob Ader as the founding father of psychoneuroimmunology rather than one of several founding fathers? Several reasons come to mind. First, Bob recognized the importance of the conditioning studies within the context of integrated physiological systems that maintain homeostasis. That is, he understood that "in the real world," the immune system does not operate as an autonomous agency of defense. More importantly, Bob did not keep this recognition to himself. Early on, he proselytized for this emerging field at meetings of various behavioral and neuroscience societies and at other meetings in the U.S. and abroad.[3] He already had a stellar reputation as a behavioral psychologist and psychosomaticist, so people in these fields listened and accepted[4]—unlike most immunologists at the time, who listened with outright disbelief if not healthy skepticism. Second, Bob also had the simple but brilliant idea of inviting those scientists who had been gathering data about

[3] Presentations at immunological societies and to immunologists at various universities fell to me, and I proselytized with what I hope was a fervor equal to Bob's.

[4] His earlier research investigated, among other things, the impact of prenatal maternal handling and differential housing on emotionality, plasma corticosterone levels, and susceptibility to gastric erosions. I remember that when Bob first read Marshall's papers of the mid 1990's that proposed a causal association of *Helicobacter pylori* with peptic ulcers, he immediately realized the implications of the fact that everyone with intestinal *H. pylori* does not develop ulcers. This realization offers some insight into how Bob Ader viewed mind/body physiology and "stress." Readers might also be interested in reading Levenstein (1998).

many facets of the CNS-immune system connection to contribute chapters to a book he called *Psychoneuroimmunology* (Ader, 1981a). This compilation — the first of its kind— coalesced the field. Furthermore, titling this book *Psychoneuroimmunology* served to add this word to the lexicon of science. Now there was a single descriptive word (and the simple acronym of PNI[5]) to categorize the study of interactions among behavior, the nervous system (including, of course, the endocrine system) and the immune system. The use of "psychoneuroimmunology" caught on and even engendered minor territorial skirmishes with those who preferred the even more cumbersome psychoneuroimmunoendocrinology or neuroimmunomodulation (which, when attached to the name of a society, made Bob query "neuroimmunomodulation of *what*?").

I don't believe that Bob thought of himself as particularly clever when he coined the word psychoneuroimmunology[6]. In his view, it was a logical choice. George Solomon had used the word Psychoimmunology in the 1960s to describe his research (Ader, 1990), and the International Society of Psychoneuroendocrinology and its journal, *Psychoneuroendocrinology*, had been established in 1969 and 1975, respectively. Bob told me that his choice only involved substituting immunology for endocrinology.

Of course, two other reasons for thinking of Bob as the founder of psychoneuroimmunology were that he established the journal *Brain, Behavior and Immunity*[7] and assumed a leadership role in forming, and then guiding, the Psychoneuroimmunology Research Society (PNIRS) during its early years as its

[5] Bob wasn't a big fan of this acronym because he felt it could somehow cheapen or demean the field (i.e., no one uses acronyms for any other serious scientific research discipline). However, he lost this battle.
[6] I believe the word, psychoneuroimmunology, received its baptismal use in Bob's presidential address at the annual meeting of the American Psychosomatic Society (Ader, 1980).
[7] He chose this name because it was euphonious and because it included behavior, which, in his vision, was an important aspect of the journal's contents.

President. Bob was highly, but fairly, critical of scientific submissions to *BBI* but never brutally so, even when he received a manuscript that was unchanged from one that he had previously rejected for another journal. Neither was Bob overly concerned when some disgruntled colleagues whose manuscripts were repeatedly rejected claimed that the journal was being run by the "Rochester mafia."

> Nick Hall: *You also demanded that PNI remain on the high road by establishing an exceptionally high standard for the study of the brain, behavior and immune system. It would have been so easy to accept the large number of poorly conceived papers that were submitted in the early days of BBI. Instead, you insisted on rejecting more papers than were accepted even though the continuation of the journal was in jeopardy when deadlines for various issues were missed due to lacking enough articles. Thank you, Bob, for nurturing PNI into an endeavor we can all be proud of.*
> Steve Cole: …th*e role you played as founder and editor of the field's defining journal really consolidated PNI as an endeavor – creating a new scientific "community on the ground" to help realize the implications of the new "facts on the ground" that you and the others began to recognize in the late 1970's."*

Bob knew the vital role he played in establishing a new field. Yet he never flaunted this role even when it might have served him personally. He didn't have to — his scientific contributions were known worldwide, as were his honesty and integrity. Formal recognition included: his appointment as the George L. Engel Professor in Psychiatry and as the Dean's Professor of Psychiatry at the URMC; receipt of an honorary medical degree from the University of Trondheim in Norway (1992) and an honorary D.Sc. degree from Tulane University (2002); and the establishment of the Robert Ader New Investigator Award by the PNIRS.

Bob wrote with a simple elegance—clarity was all-important. Data-rich publications, including Bob's, are formulaic and therefore, rather dull from a literary perspective. But given the opportunity to break away from the format of a scientific paper, Bob's writing became, at least to me, an engrossing narrative. For those of you interested in this facet of his writing, I suggest you read two papers. The first is his presidential address to the American Psychosomatic Society (Ader, 1980). The second is a book chapter entitled *Historical perspectives on psychoneuroimmunology* (Ader, 1996).[8] Reading this chapter will not only familiarize you with the history of our field but it will reveal the humility of this man as well as what a good scientific writer he was. Parenthetically, the information about each of the early contributors to our field was the outcome of Bob's interviews with the contributors themselves.

For the past few years, deteriorating health made it impossible for Bob to attend the annual meetings of the PNIRS. I know he missed these opportunities to connect with old friends and make new ones. If he had been able to reconnect, I'm sure he would have told folks about his latest translational research on exploiting partial reinforcement and conditioning in pharmacotherapeutic regimens. He might also have shared with you the new clinical collaborations he was developing within this area of placebo research, and wondered whether you might be interested in collaborating. He probably would not have mentioned the reputation he was establishing in this area. Neither would he have mentioned the impact he has already had on shaping the research careers of some physicians. He wouldn't have boasted in this way, but that doesn't stop me and others from doing it.

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[8] The URL for downloading this important paper is: http://psiconeuroinmunologia.mx/uploads/2/9/2/1/2921728/historia_de_la_pni_por_dr._robert_ader.pdf.

John Bisognano: *I am trying to learn an entirely new field and soon will be persuading the hypertension community on how this may be a good idea. I like to be exploring a new avenue of treatment and will always look back at our meeting at Tim Horton's as a pivotal moment in my life. Not only will we be exploring a new treatment for hypertension (as the present treatments don't work for 50% of the people), but my career now includes an R01 and I'm getting advice! For this, I remain extraordinarily grateful.*
Steve Lamberti: *In preparation for our meeting, I came up with a set of questions about who would be PI, how we would decide upon the order of authorship of manuscripts, and other related items. As I started to broach these questions, you simply smiled at me and said, "Steve, I don't need another publication or grant— you can be PI and first author on everything." I was absolutely floored by this. You were offering me precious gems of knowledge, with no expectation other than I accompany you on this adventure!*
Michael Perlis: *Bob, you said: "I don't need such stuff (being PI) or want the responsibility… what I want is to test the idea in as many applications as I can with people from various fields taking point." Well you don't walk from an offer like that: I said, "OK. Let's get to work." So we started meeting regularly. We worked through the oddities of co-writing, and we produced a grant that on its second submission (then a 3 cycle review process) got a perfect score (1st percentile). Wow! Life changed because of you.*

Among Bob's scientific colleagues were those with whom he shared a close friendship. I, for one, will miss our long talks during sushi lunches, or in a rented boat not catching fish, or while sharing a room at a meeting in an exotic location.

Jan Moynihan: *People have written letters to you with words describing you such as: integrity, life changing, pioneering, leader. My words to describe you would also include: kind, caring, a passionate and protective father and husband, a true and dear friend, and, of course, a killer photographer. And, maybe even sometimes a little*

goofy…if I were nearly as organized as you, I would be able to unearth the acceptance letter for my first BBI paper that you wrote to me in crayon!

A week or two before Bob died, we were chatting on the telephone. He was filling me in on his health status and on some professional developments. He told me that an Elsevier editor who was newly charged with developing future editions of *Psychoneuroimmunology* had proposed that if Bob consented to having his name used in future editions, Elsevier was prepared to pay royalties according to a particular schedule. "Sort of like the classic textbook, *Gray's Anatomy*," Bob was told. I don't know if any formal agreement was signed, but regardless, to me it will always be Ader's *Psychoneuroimmunology*.

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