

William E. Paul, M.D., AAI '67

June 12, 1936–September 18, 2015

President, The American Association of Immunologists, 1986–1987

AAI extends condolences to the family, friends, and colleagues of William E. ("Bill") Paul, M.D., AAI '67, who died on September 18. The following remembrance was authored by Paul protégé and colleague Fred D. Finkelman, M.D., AAI '76, with help from former Paul fellows Robert Seder, M.D., AAI '94, and Ulus Atasoy, M.D., AAI '07. AAI gratefully acknowledges the submission.

With the death of Bill Paul on September 18 from acute myelogenous leukemia at age 79, we have lost a great immunologist and a great person.

Bill was a product of the Eastern European Jewish migration to New York City; he was educated in the city's public schools, including Erasmus High School and Brooklyn College, where reading a book of essays by Michael Heidelberger initiated his interest in immunology, and SUNY Downstate Medical School, where he had his first taste of biological research. A summer research opportunity in 1959, prior to his last year of medical school, introduced Bill to NIH, where he would spend the great majority of his career. Bill's genius as an investigator surfaced early. Work with Alan Cohen during Bill's residency in internal medicine led to Bill's first paper -- a study of amyloid particles that was published in *Nature*. Bill's two years as a clinical associate in NCI's Endocrinology Branch (1962-64), which satisfied his military obligation, led to an additional paper in *Nature*, as well as to the first radioimmunoassay for thyroid stimulating hormone.

Bill's research career accelerated and became focused on immunology in 1964, when he joined the lab of Baruj Benacerraf, then at NYU. Bill's work at this time established a technique for evaluating the ability of guinea pig T cells to respond to specific antigens and refined previous evidence that B and T cells "see" antigen differently. Both observations would be critical for his initial independent studies, which began four years later when Bill moved with Baruj to NIH. There, Baruj became head of the Laboratory of Immunology (LI) and Bill became a senior investigator in that laboratory. Two years after that, when Baruj moved to Harvard, Bill, at age 34, was appointed head of the LI, a position he retained until his death.



William Paul

Bill's focus as lab chief at LI continued to be on how T cells "see" antigen. Studies in guinea pigs and mice with Ira Green, Ethan Shevach, Alan Rosenthal, and Ron Schwartz demonstrated that the Ir gene products, which had been shown to control the ability of T cells to respond to certain defined antigens, were MHC class II molecules. This evidence was crucial for later discoveries by Emil Unanue that defined antigen processing and MHC-mediated presentation of antigen-derived peptides to T cells. Work by Bill and his team also contributed importantly to the conclusion that the T cell antigen receptor (TCR) differed from surface immunoglobulin, the

B cell receptor for antigen. This conclusion promoted the quest to identify the TCR, which was initiated by Mark Davis while a post-doc in Bill's lab, and culminated in independent work done by Mark and his team (Steve Hedrick, David Cohen, Ellen Nielsen) after Mark became an independent investigator at NIAID.

As the LI developed under Bill's leadership, additional areas of fruitful investigation developed. Studies with John van Boxel, Ira Green, Bill Terry, Donna Sieckmann, Dick Asofsky, and Don Mosier established the co-expression of membrane IgM and IgD as B cell antigen receptors, and clearly demonstrated that membrane Ig was an important signaling molecule for B cells in addition to being a means for focusing antigen onto these cells. Studies with Rafi Sharon, Phil McMaster, John Inman, Don Mosier, Jimmy Mond, and Irwin Scher established the classification of two types of T cell-independent antigens and the recognition that they activated B cells through distinct mechanisms.

Perhaps because of my own interests, I think that Bill's most important contribution to immunology began with his identification, working with his post-doc Maureen Howard, of IL-4 (then called BSF-1) as a soluble, T cell-produced factor that promoted membrane Ig crosslinking-induced B cell proliferation. After Junichi Ohara purified IL-4 and produced a neutralizing mAb against it, studies with Ellen Vitetta, Bob Coffman, Cliff Snapper, Graham LeGros, Zami Ben-Sasson, and my own group showed the importance of this cytokine as

an isotype switch factor for the induction of murine and human IgE and, to some extent, murine IgG1 responses; as a critical stimulus for the development of Th2 responses; and as an essential stimulus (with the related cytokine, IL-13) for host protection against many multicellular parasites. Some of the same investigators plus Alan Sher, working with Bill, helped establish the opposing roles of IL-4 vs. IL-12 and IFN- γ in isotype switching and T cell differentiation, while studies with Bob Seder, Marshall Plaut, and Booki Min established the importance of basophils as IL-4-secreting cells. In addition, a review of IL-4 biology by Bill and Bob Seder first proposed the concept of the immunological synapse.

Studies later in Bill's career continued to define the importance of IL-4 and improved understanding of IL-4-related mechanisms: this has included work with Tomo Yoshimoto that demonstrated rapid IL-4 production by NKT cells; work with Achshah Keegan, Keats Nelms, and John Ryan that elucidated Stat6-independent IL-4 signaling mechanisms; studies with Hidehiro Yamane that established the positive feedback regulation of Th2 cell differentiation; work with Jeff Zhu and Ryoji Yagi that studied the transcriptional regulation of this process; and studies with Lilly Guo that demonstrated probabilistic control of T cell IL-4 expression. Other later studies included the demonstration, with Zami Ben-Sasson, of the critical role of IL-1 β in the induction of T cell responses, work with Booki Min and Josh Milner on the regulation of autoimmunity, immune homeostasis, and inflammation, and work with Lilly Guo on interactions between innate and adaptive immunity.

Although Bill's scientific discoveries have had an enormous impact on our knowledge of the immune system, I believe that his contributions as an educator and leader have been even greater. Bill and his colleagues at the Laboratory of Immunology contributed to the training of an enormous number of immunologists who have done important independent work and gone on to major positions in academia and industry. I'm extraordinarily proud to be on a list that includes Joe Davie, Charlie Janeway, Jack Stobo, Ethan Shevach, Zami Ben-Sasson, Don Mosier, Ben Schwartz, Philip Cohen, Ron Schwartz, Kim Bottomly, Michael Harrison, Jimmy Mond, Michael Gelfand, Constantin Bona, David Thomas, Irwin Scher, Mark Davis, Laurie Glimcher, Maureen Howard, Tony DeFranco, Steve Hedrick, Wayne Yokoyama, John Kung, Kenji Nakanishi, Takashi Saito, Junichi Ohara, Melissa Brown, Reinhard Burger, Cliff Snapper, Bob Seder, Tomo Yoshimoto, Achshah Keegan, Keats Nelms, John Ryan, Josh Milner, Jeff Zhu, Hidehiro Yamane, Lilly Guo, Evelyn Rabin, and Booki Min. Bill's achievements in this area were honored by his receipt of the AAI Excellence in Mentoring Award in 2014. Although Bill would have attributed most of this success to the high intellectual quality and strong work ethic of his post-docs, he deserves tremendous credit himself. Bill

ran an informal lab where he was on a first name basis with everyone. He did not micromanage his students, but taught the imperative of choosing projects that address an important goal or question and to re-evaluate periodically to ensure that the potential benefit is worth the effort. His advice on experimental design, data interpretation, and discerning what to do next reflected his great intelligence, mental quickness, experience, and knowledge of the field and its practitioners; his articulateness and way of talking to people made fellows look forward to data sessions with Bill and feel better afterwards, even when the work was not going well. Relationships with Bill persisted after completion of fellowships, much to the advantage of former fellows. Bill's influence as a teacher spread well beyond his lab, with his introduction of *Fundamental Immunology*, still the premier comprehensive immunology text, in 1982 and the introduction of *Annual Reviews in Immunology*, now in its 31st year and perennially the immunology journal with the highest impact factor.

The same qualities that made Bill a great mentor, combined with his total and transparent honesty and moral integrity, made him a great leader of both the Laboratory of Immunology and outside organizations. Bill is one of the few who have served as president of both the American Society of Clinical Investigation (1980) and the American Association of Immunologists (1986-87). As AAI president, he strengthened the relationship between the AAI and *The Journal of Immunology (The JI)* and supported the establishment of the Clinical Immunology Society. Bill's work for foundations included service on behalf of the Howard Hughes Medical Institute as one of three advisors in immunology and as a member of its Scientific Review Board and Medical Advisory Board, as well as service to the Lupus Research Institute that included chairing its Scientific Advisory Board. Bill's most prominent and important service to the immunology community, his nation, and the world, however, was his service as the first "AIDS Czar"—Director of the Office of AIDS Research—from 1994 to 1998. This period was marked by the calming of contentious and conflicting goals, encouragement of the basic and translational research and collaborations between academia, the NIH, and the pharmaceutical industry that promoted the development of highly active antiretroviral therapy, and the founding of the NIH Vaccine Research Center. Bill's September 22 obituary by Sam Roberts in *The New York Times* quotes Mark Harrington, executive director of the Treatment Action Group, as saying that Bill was "responsible for saving millions of lives and preventing millions of infections" and characterizing Bill as "an unheralded hero of the AIDS epidemic."

Bill's great accomplishments attracted commensurate honors, some of which include the Founder's Prize of the

See *In Memoriam: William Paul*, next page

William E. Paul, M.D., AAI '67 (Continued)

Texas Instruments Foundation (1980), the AAI Lifetime Achievement Award (2002), election to membership in the National Academy of Sciences (1982) and its Institute of Medicine (1990), and fellowship in the American Academy of Arts and Sciences.

In addition to Bill's many commitments to science and humanity, he stood out as an exemplary husband, father, and grandfather. He met his wonderful wife, the former Marilyn Heller, in college. They married during his third year of medical school and their love for each other continued unabated until the end. Bill's two sons, Matthew and Jonathan, were a source of great pride. No loss affected Bill and Marilyn as deeply as the death of their young grandson, Julien, from a variant of acute myelogenous leukemia. Bill's love for his grandchildren was so great that it was noted at his funeral that he was able to watch the "Penguins of Madagascar" video five times with one of his granddaughters without falling asleep!

Many of us who regarded Bill as our immunologic father thought that he would continue his research forever. Certainly, we saw no decrease in the quality of his scientific publications and observations. He rejected his former fellows' plan to honor him with a research day at NIH on his 75th birthday because he was afraid that some might consider this a prelude to retirement. Similarly, Bill opened his prefatory article in this year's *Annual Review of Immunology* (from which much of the detail in this memorial was derived) with the comment that "It's too early [to write such an article]; I am busy thinking about new experiments, not about summing up a lifetime in science." Tragically, several years ago Bill developed a myeloid dysplastic syndrome, which mutated this year into acute myeloid leukemia that was complicated by an EBV-related B cell lymphoma. Bill elected to receive a stem cell transplant and commuted with Marilyn between the lymphoma service at NIH and the leukemia service at Memorial Sloan-Kettering for treatment. Many of us, following Bill's progress and disappointments on Marilyn Paul's blog on CaringBridge, were amazed at his continuing to direct research in his lab as well as his continuing enjoyment, with Marilyn, of plays, concerts, art museums, walking tours of NYC architecture, dining, and time with friends and family, while he received arduous chemotherapy. Unfortunately, relapses and complications of therapy kept postponing the planned



Photo: Ronald Germain

transplant, until Bill developed a final, rapidly lethal pulmonary complication. Bill's funeral service at Temple Micah in Washington, DC, included eulogies by Tony Fauci, who appropriately described Bill as "the immunologist to the world," Ron Germain, who elegantly summarized Bill's contributions and the joys of working with him, and Laurie Glimcher, who recalled how far ahead of his time Bill was in supporting a post-doc who came to his lab in her last month of pregnancy.

In the last paragraph of what turned out to be his valedictory article in the *Annual Review of Immunology*, Bill mentions the

ancient Jewish concept of *tikun olam*—the idea that God purposely left the world unfinished, to give humans the responsibility and opportunity to complete and perfect creation. Bill goes on to state "A career in immunology certainly qualifies!" In Bill's case, this was obviously true. One final coincidence: on the day Bill died, I received my copy of his most recent book, *Immunity*, a combined description of immunology for the educated layman and memoir of Bill's life as an immunologist. For me in my sadness, this carried the happy message that Bill lives on in his accomplishments, his thoughts, and his personal and scientific families.

Bill Paul's leadership of AAI (President, 1986-1987) was the culmination of his tenure on the AAI Council commencing in 1981. An AAI member since 1967, he also served on many AAI committees including the Program Committee (1970-1972; 1977-1980; 1980-1981, as co-chair), Nominating Committee (1973-1974, as chair; 1999-2000), Committee for Travel Awards to the Third International Congress (1974-1977); Finance Committee (1982-1984; 1990-1992); and Awards Committee (1993-1996). He also served as an Associate Editor (1971-1975), Section Editor (1975-1978), and on the Editorial Board (now the Publications Committee) (1979-1984) for *The JI*. [Bill's CV included over 130 articles published in *The JI*; the most recent was published in the February 1, 2015, issue.] Bill represented AAI in national and international organizations, including the Federation of American Societies for Experimental Biology Board (1985-1988) and the International Union of Immunological Societies General Assembly (1986-1987).

To view Paul's 2012 interview for the AAI Oral History Project, visit his profile in the History section of the AAI site: http://www.aai.org/About/History/Notable_Members/Presidents/Paul_William.html.