

Obituary

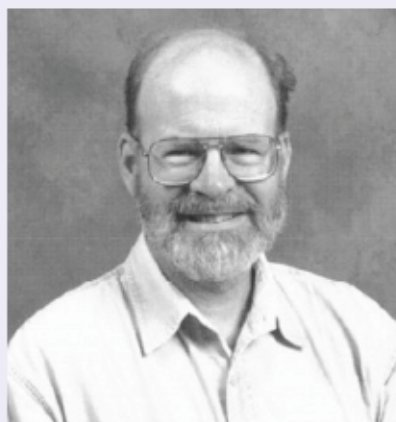
Charles A. Janeway Jr (1943–2003)

Charles A. Janeway Jr, professor of immunobiology at Yale University School of Medicine in New Haven and one of the pre-eminent modern immunologists, died on 12 April 2003 of lymphoma. Most scientists only dream of contributing to a paradigm shift — Janeway personally initiated one. Most focus their research efforts in one narrow area of specialization — Janeway's work ranged over the breadth of immunology. Most influence the training of only a small cohort of students, but Janeway's contribution to education reached thousands, at all levels of sophistication.

In 1989, Janeway launched the idea that, in addition to the ability of the immune system to discriminate between 'self' and 'non-self' molecules, there is a second law of immunology. He reasoned that there must be mechanisms to ensure that an immune response is not only specific, but is also appropriate. In other words, the immune system should respond vigorously and effectively to antigens associated with potentially pathogenic microorganisms, and ignore or devote little energy to fundamentally 'bland' antigens, even if they are foreign. In a seminal paper, Janeway postulated that the immune system would 'know' what is appropriate because of cues provided by the microorganism bearing the antigen, and he introduced the terms 'pathogen-associated molecular patterns' for these cues, and 'pattern-recognition receptors' for the postulated elements on immune cells that would sense the microbial signals.

Now, it is one thing to have a great idea and another to prove it. With Ruslan Medzhitov, a postdoctoral fellow and then colleague at Yale, Janeway showed that mammalian relatives of the Toll protein — a key player in the inflammatory response in fruitflies — constitute one set of pattern-recognition receptors. Indeed, we now know that the Toll-like receptors recognize a wide array of structures associated with various pathogens, including lipopolysaccharide (found in the cell wall of many bacteria) and double-stranded RNA. Recognition of these molecules by key components of the innate immune system, notably dendritic cells, sets off intracellular signals that equip the cells to direct the priming and differentiation of cells of the adaptive immune system. This system can then deal optimally with the type of pathogen that induced the response.

Janeway was the product of a distinguished medical family. His great-



Immunologist who postulated a second law of immunology

grandfather had been health commissioner of New York City; his grandfather described 'Janeway's lesions', a key sign of subacute bacterial endocarditis (infection of the inner surface and valves of the heart); and his father was physician-in-chief of the Boston Children's Hospital and one of the founders of the modern study of immunodeficiency diseases. Janeway followed in this tradition professionally, though not sartorially — despite his Brahmin background, he was most comfortable in a workshirt and jeans, wearing his trademark red hat and looking more like a holdover from the flower-power days of the 1960s than the Yale professor he was for so many years.

Janeway's education was critically influenced during his medical school days by Hugh McDevitt, who advised him to work in England with immunologist John Humphrey. Janeway credited the two years he spent with Humphrey — from 1965 to 1967 — as being extraordinarily influential in shaping his life as a scientist. After clinical training, he came to the Laboratory of Immunology at the National Institute of Allergy and Infectious Diseases (NIAID) in 1970, as a postdoctoral fellow with one of us (W.E.P.). Janeway was of that imaginative breed of scientist for whom the right environment and largely being left alone constituted the best training.

After leaving the NIAID, a sojourn at the University of Uppsala was followed by an appointment in 1977 to the pathology department at Yale, and then to the immunobiology section. In New Haven, Janeway married another immunologist, Kim Bottomly, whom he had met at the

NIAID. This relationship was a deep one, encompassing home, family and science. In particular, Janeway credited his wife with encouraging him to articulate his thoughts about the connection between the innate and adaptive immune systems.

While best known for bringing this connection to the fore, Janeway also made substantial contributions to a range of other topics. He championed the notion of the CD4 and CD8 proteins as 'co-receptors' in the physically intimate interaction between MHC molecules (which present antigens to immune cells) and the T-cell antigen receptor. He made advances in our understanding of cell-mediated autoimmune disease, T- and B-cell tolerance of self molecules, the role of co-signalling in T-cell activation, thymocyte selection, and the biochemical basis of T-cell recognition of antigen-MHC complexes. He collaborated with Bottomly in her discovery of two distinct functional subsets of CD4-expressing cells, which she called T inflammatory and T helper cells — now known as Th1 and Th2 cells.

Janeway was a superb teacher, and for many years ran the Yale immunology course for medical students. He used his lecture notes for this course to develop *Immunobiology*, which has become one of the major immunology textbooks. This text was a central part of Janeway's intellectual life, and even while ill he brought out new editions that kept pace with the rapidly changing face of modern immunology. Similarly, although the idea of a link between adaptive and innate immunity came to him before he was diagnosed with lymphoma, virtually all the major research that established the concept was done afterwards. His underlying love of the field — of the wresting, through experiment, discussion and thought, of each new insight into the immune system and the cells that ultimately turned against him — always showed through.

In 1998, Charlie opened his presidential address to the American Association of Immunologists with a recitation of Robert Frost's "The Road Not Taken". He used it to make the point that "the road less traveled by" was emblematic of the choices one makes that define one's life — in his case, his decision to investigate the link he had postulated between innate and adaptive immunity. For Charlie, those choices led to a legacy that will continue to enrich modern science. **William E. Paul and Ronald N. Germain** *William E. Paul and Ronald N. Germain are in the Laboratory of Immunology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20892, USA. e-mail: wpaul@niaid.nih.gov*