Ten Get the Call to Stockholm

This year's crop of Nobelists are honored for two new states of matter, a double-key model of immune-cell triggering, and the economic implications of honesty

UNRAVELING IMMUNE-CELL MYSTERIES

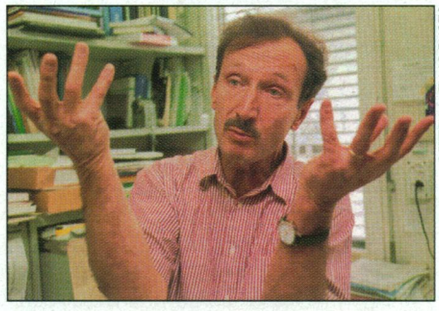
When good scientists step into a field from the outside, their views, not yet conditioned by the field's standard thinking, can sometimes really shake things up. That was the case with this year's winners of the Nobel Prize in physiology or medicine, awarded to Australia's Peter Doherty and Switzerland's Rolf Zinkernagel for their insights into the inner mechanics of the immune system.

Doherty initially had his eyes set on veterinary medicine, and Zinkernagel had planned to become a surgeon. Instead, while working during the 1970s at the John Curtin School of Medical Research in Canberra, Australia, they came up with a simple explanation of how the immune system's killer T cells accomplish a key step in fighting off viral infections: distinguishing between virus-infected and normal cells, so that the infected cells can be selectively eliminated. The investigators found that the killer cells recognize not just the virus, but also certain cellular proteins, called histocompatibility antigens, whose function—until then—had been a mystery.

Doherty and Zinkernagel "came out of the blue and astonished everybody," says Harald von Boehmer, an immunologist at the Institut Necker in Paris and himself a pioneer in the field. "They opened up a new chapter in immunology." They also provided guidance to researchers seeking to understand and combat diseases ranging from cancer and AIDS to autoimmune conditions, such as rheumatoid arthritis and diabetes, in which the body erroneously attacks its own tissue.

When Doherty and Zinkernagel began their work, immunological dogma held that viral or bacterial particles alone were sufficient to trigger an immune-cell attack. "No one had really thought that it was the body's own cells," recalls Doherty, now chair of the department of immunology at St. Jude Children's Research Hospital in Memphis, Tennessee. "Everyone just assumed that it was the virus itself that caused the immune response." The histocompatibility proteins, for their part, were known only as the triggers of transplant rejection. While everyone assumed that they must have a normal function, no one knew what it was.

Doherty and Zinkernagel did not set out to address either problem. Thrown together by chance in the same lab because of lack of space, they joined forces to try to find out what causes the lethal brain destruction of mice infected with lymphocytic choriomeningitis virus (LCMV). They thought that the brain damage might be caused by killer T cells responding to the virus, and wanted to develop an assay testing that.



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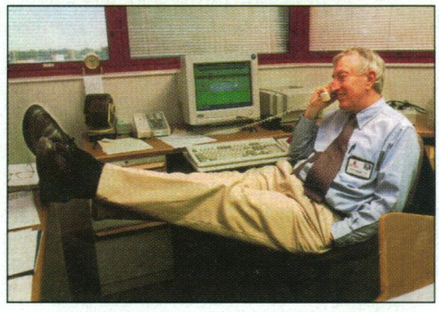

MICHAEL MCMULLAN/AP PHOTO

Dynamic duo. Luck and insight brought Rolf Zinkernagel *(top)* and Peter Doherty the medicine Nobel.

For their assay, Doherty and Zinkernagel mixed the brain fluid of infected mice, which contained T cells, with mouse cells that were separately infected with LCMV. As expected, the T cells did kill the infected cells, and, thus, the assay worked. But that was only by chance, as it turned out, because the researchers happened to test the T cells against LCMV-infected cells of the same strain, mainly because that was what was available at their institution.

Even then, though, Doherty and Zinkernagel suspected that the assay might not have worked with T cells of a different strain, a notion that was further boosted when the two investigators came across a report by immunologist Hugh McDevitt, then at Harvard University, and his collaborators linking immune responses to the genes of the major histocompatibility complex (MHC), which encode histocompatibility proteins.

To see whether these "self" proteins affected the killer-cell attacks, Doherty and Zinkernagel paired combinations of T cells and infected cells bearing various MHC proteins. On finding that the T cells only kill MHC-matched infected cells, the researchers concluded that an attacking T cell had to recognize two signals on a viral-infected cell: one from the virus, and the other unique to the cell. "It was a wonderful example of how certain things cannot be planned," says Zinkernagel, now director of the Institute of Experimental Immunology at the University of Zurich, Switzerland. "Absolutely, this was a miracle of chance."

The discovery took more than good luck, however. Other immunologists had already noted pieces of the answer, points out Ronald Schwartz of the National Institute of Allergy and Infectious Diseases. But it was Doherty and Zinkernagel who "made that intuitive leap," says Schwartz. "They [proposed] a model, and it turned out to be the correct model."

Still, it took more than 2 decades, many other researchers, and the advent of molecular biology techniques to work out all the intricacies of the T cell recognition model. Now the research is moving into a new phase, as investigators try to use the information to come up with vaccines against cancerous or HIV-infected cells, or rein in the overzealous T cell responses that can lead to autoimmune diseases. As the Nobel Prize has amply confirmed, Doherty and Zinkernagel are outsiders no longer.

–Trisha Gura

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A CAPTIVATING CARBON FORM

Clues to hidden treasures can be easy to overlook. In the mid-1980s, for instance, many chemists thought they knew all there was to know about carbon. As it turned out, though, one of its most elegant forms was still unrevealed. Over the years, numerous researchers had noted an odd finding, that under certain conditions carbon atoms had a tendency to cluster in groups of 60. But no one stopped to take a second look.

No one did until September 1985, that is, when a group of American and British researchers dived into the mystery and discov-