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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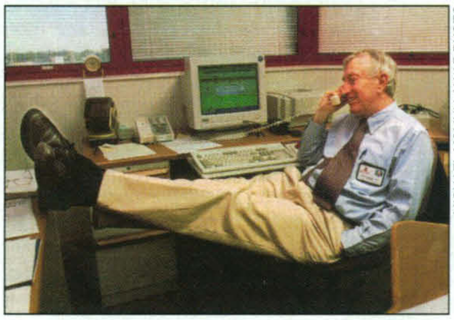


MICHAEL MCMULLAN/AP PHOTO

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

Trisha Gura is a free-lance writer in Cleveland.

A Captivating Carbon Form

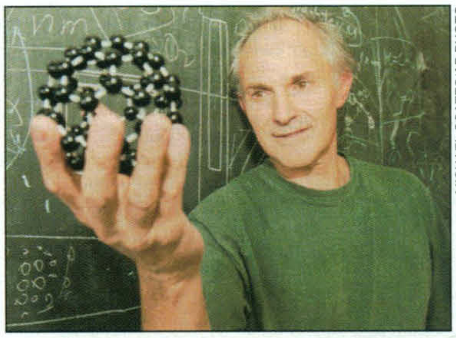
Clues to hidden treasures can be easy to overlook. In the mid-1980s, for instance, many chemists thought they knew all there was to know about carbon. As it turned out, though, one of its most elegant forms was still unrevealed. Over the years, numerous researchers had noted an odd finding, that under 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 discovered an entirely new class of all-carbon molecules shaped like intricate, spherical cages. Last week, the finding earned the team's leaders—Richard E. Smalley and Robert F. Curl Jr. of Rice University in Houston, and Harold W. Kroto of the University of Sussex in Brighton, United Kingdom—this year's Nobel Prize in chemistry. The discovery of "buckyballs" "[has] led to a completely new field of materials chemistry," says Charles Lieber, a professor of chemistry and applied physics at Harvard University. Today, researchers are investigating the all-carbon cages, also known as fullerenes, for use in applications ranging from new superconductors and catalysts to ultrasmall electronic devices.

Prior to the discovery, researchers knew of only two naturally occurring forms of crystalline carbon. There was graphite, the gray "lead" in pencils, in which neighboring atoms are arranged in sheets of hexagons, and diamond, in which neighboring carbons are grouped into pyramids. Smalley, Curl, and Kroto set out to create a noncrystalline form—but what they had in mind was nothing like a buckyball. At Sussex, Kroto was studying star dust. He had theorized that the outer atmosphere of red giant stars would produce a bounty of long carbon chains and was interested in reproducing them in the lab. As it happened, Smalley and Curl had just the right equipment. Smalley had built a machine that vaporized materials with laser light in the presence of an inert gas, and they were using the apparatus to study how semiconductor and metal clusters grew out of the vapor.

Kroto learned of the cluster-building machine when he met Curl at a conference in the spring of 1984, and a year and a half later, their collaboration got under way. Shortly after the team began vaporizing carbon, the researchers and their graduate students, James Heath and Sean O'Brien, noticed a spike in the readings from their mass spectrometer, indicating that molecules with a combined mass of 60 carbons were forming in the vapor. Oddly, recalls Curl, "the peak was about 20 to 25 times as strong as the others." Even more oddly, when the researchers allowed the carbon clusters to cook in the machine with other molecules at high temperatures, the 60-carbon clusters proved to be "extremely unreactive," says Smalley.

That left them with a mystery. Sheets and pyramids of carbon are only stable when laced together in huge, continuous structures—a diamond, for instance. When a carbon structure has as few as 60 atoms, the many dangling bonds at the edges of the sheet or pyramid make the structure highly reactive. "We were looking for a structure of 60 carbon atoms that didn't want to react any further," says Smalley. That meant coming up with an architecture without dangling bonds.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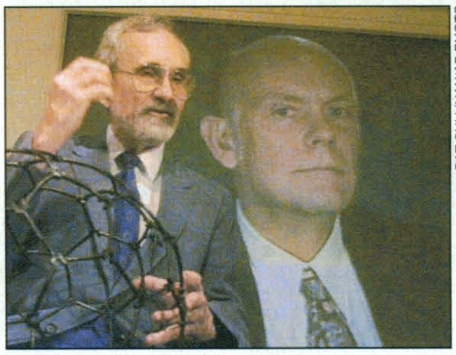
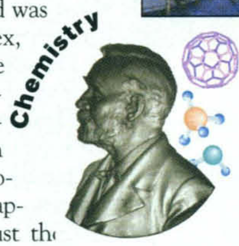

PAT SULLIVAN/AP PHOTO

Buckyboost. Kroto *(top)* with winning molecule. Curl *(above, left)* with Smalley *(above, right)* on screen.



Near the end of their experimental run, the researchers hit on the crucial idea: that an arrangement of carbons in a pattern of hexagons and pentagons would cause the sheet to curl into a closed sphere. One night, Smalley stayed up late and built a paper model of a possible structure with a soccer-ball shape. The next morning, he showed it to his colleagues, and Curl and Kroto set out to determine if it obeyed the normal rules of carbon bonding. "I remember a shout for joy when they managed to do it," says Smalley. Within days they had submitted a paper on the topic to *Nature*.

Initially, many scientists were skeptical of buckyballs. But the structure was confirmed in 1990, when a team of physicists—led by Donald Huffman at the University of Arizona and Wolfgang Krätschmer from the Max Planck Institute for Nuclear Physics in Heidelberg, Germany—succeeded in synthesizing measurable quantities of fullerenes, which made it possible to study samples with structure-determining tools, such as x-ray diffraction machines.

Since then, the field has "exploded" into new areas, says Lieber, as researchers have discovered ways to both insert atoms into the cages and tack them onto the outside in an effort to make new materials with unique electrical, optical, and magnetic properties. Other teams are focusing on related tube-shaped fullerenes, called nanotubes, for possible uses in everything from tips for scanning probe microscopes to arrays of mini-electron guns for flat-panel displays. Says Marvin Cohen, a physics professor at the University of California, Berkeley, "There's so much action in the physics and chemistry of these things that we [will be] busy for a lot of years to come."

–Robert F. Service

A Cold Elixir for Physics

On the day before Thanksgiving in 1971, a graduate student in Cornell University's low-temperature laboratory monitored the pressure in a supercooled cell containing a mixture of liquid and solid helium-3. The pressure changed steadily as the temperature fell toward absolute zero, until it reached a few thousandths of a kelvin. At that point, the student—Douglas Osheroff, now a professor at Stanford University—noticed an unexpected shift in the rate of pressure change. Osheroff carefully reported the effect to his advisers, Cornell's David Lee and Robert Richardson. Months later the team realized what that shift had meant: It marked helium-3's transition from an ordinary fluid to a superfluid—a strange, frictionless, quantum-mechanical substance.

The finding struck low-temperature physics "like a lightning bolt," says Russell Donnelly of the University of Oregon. The lockstep atomic interactions required to make superfluid helium-3, says Philip Anderson, a theorist at Princeton University, meant the discovery "really was a milestone in our understanding of complex, many-body systems." The work's implications are still reverberating today, he says, in fields including cosmology and high-temperature superconductivity.

And in a recognition that Donnelly calls "way, way overdue," the discovery reverberated in yet another way in Osheroff's house in the wee hours of 9 October. "This fellow from Sweden called up, and I didn't recognize the accent. He said, 'Is Douglas Osheroff there?' I said, 'Yes, and it's 2:30 in the morning.' " Osheroff woke up quickly. Together with Lee and Richardson, he had won the 1996 Nobel Prize in physics.

The historical roots of the work go back well before 1971. A superfluid state of helium's most common isotope, helium-4, was first produced in 1938 by cooling it to about 2.2 K. The relatively accessible temperature of the helium-4 transition reflects the rules of quantum mechanics. The quantum-mechanical spins of the protons, neutrons, and electrons in each helium-4 atom add up to an integer value. That qualifies the atoms as "bosons," meaning they can all drop into the same low-energy state and move in lockstep. If the flow is gentle enough, the atoms can't absorb enough energy to jump