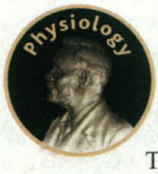
NOBEL PRIZES

Colleagues Say 'Amen' to This Year's Choices

The prize committees' decisions sometimes provoke rancor and second-guessing, but this year's laureates appear to be sure-fire choices



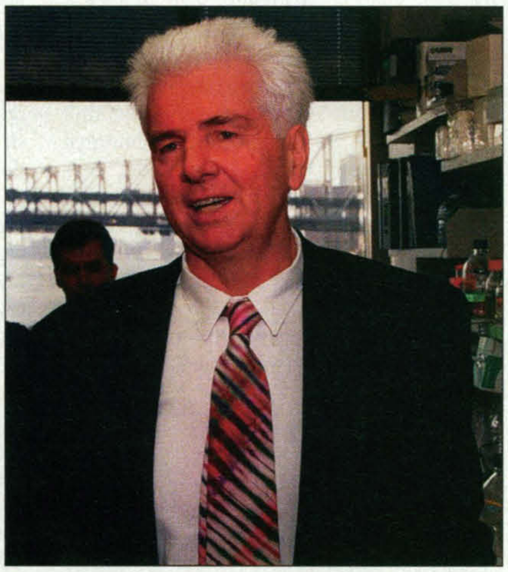
Protein ZIP Codes Make Nobel Journey

Truly great discoveries often appear obvious in hindsight. So do some Nobel prizes, including this year's Nobel Prize in Physiology or Medicine, awarded to the German-born cell biologist Günter Blobel for his insights into how the cell uses a ZIP code system of sorts to deliver thousands of proteins to various addresses within the cell.

Several recent Nobel prizes for medicine have stirred controversy; in 1997, for example, the prize recognized what many say is still a highly disputed theory that proteins called prions can act as infectious agents (see p. 660). But the current prize decision seems to have been a safe bet. Randy Shekman, a cell biologist at the University of California, Berkeley, says, "Almost all of us in the field expected this; it was long overdue." James Rothman, a cell biologist at the Memorial Sloan-Kettering Cancer Center in New York, agrees, saying that "Blobel's contributions about proteins encoding their own fate in the cell were truly monumental in scope." He adds that Blobel's concept itself seemed so obvious—"it left you with a feeling of utter simplicity"— that some biologists resisted it at first.

Just as people try to organize their belongings by devising filing systems, cells have to sort newly synthesized proteins and send them wherever they are needed: into different internal compartments called organelles or even out of the cell altogether. In the 1960s, George Palade of The Rockefeller University in New York City had found that proteins designated to be excreted pass through a sort of relay station called the endoplasmic reticulum (ER), a vast folded membrane system that looks like a deflated beach ball—a discovery that helped earn him a Nobel prize in 1974. But no one had a clue about the inner workings of this protein-sorting machinery. "Cellular transport really was something of a black box," says Wilhelm Stoffel, a molecular neurobiologist at the University of Cologne in Germany.

Blobel, who joined Palade as a postdoc in the late 1960s and has stayed at Rockefeller ever since, was captivated by this protein secretion puzzle. In 1971, together with David Sabatini, now at New York University, he formulated a simple model of how cells regulate their protein traffic: The first few amino acids in a nascent protein chain serve as an address tag that tells the cell whether or not the protein is destined for secretion and hence for import into the ER. "At first it was just a wonderful idea; it was quite a bold thing to say because nothing hinted at a signal sequence. But it was by far the best thing we could come up with," recalls Blobel.



Postmaster. Günter Blobel deciphered the intracellular address system for newly made proteins.

Only a year later a group at the Medical Research Council Laboratory in Cambridge, U.K., led by César Milstein (yet another Nobel laureate, who won the prize in 1984 for monoclonal antibody technology) found the first hints of signal sequences in one of the protein chains of antibodies. The form of the protein that had been secreted into the bloodstream, these researchers found, was a little shorter than the one that was still within cells, suggesting to Blobel that a signal sequence originally present on the protein had been trimmed away by the time it was secreted. In the following years Blobel developed a cell-free system that mimicked the cell's protein sorting pathway, so that he could identify the molecular players.

Finally, in 1975, he succeeded in deciphering the first signal sequence. At the same time he expanded the original hypothesis by proposing that the ER membrane contains a protein channel through which the proteins to be secreted sneak into the ER. Rothman, who was a postdoc at the time, still vividly remembers the "excitement in the field, when you realize biology will never be the same again."

Blobel and his colleagues then went on to pin down the various parts of the ER export system. In the early 1980s, the work culminated in their discovery both of the so-called "signal recognition protein" (SRP), which reads the ER ZIP code by binding to it in the cytoplasm, and of the receptor on ER membranes to which the complex of SRP and nascent protein chain then docks. At the same time Blobel and others showed that similar ZIP codes also serve to guide proteins to other cell organelles such as mitochondria, the cellular power plants, and chloroplasts, the site of photosynthesis in plant cells. "It's always variations on the same theme: various signals, SRPs, and docking receptors" for different organelles, Blobel explains. Finally, in the series of experiments, done in the early 1990s, that Blobel says he's most proud of, his team demonstrated the existence of the long-elusive ER channel.

Together, say many colleagues, these studies laid the foundations for modern cell biology. "Blobel was the first one to make cellular biology molecular and come up with mechanisms; before that it was merely descriptive," says Kai Simons of the European Molecular Biology Laboratory in Heidelberg, Germany. Blobel's ideas have also shed light on diseases such as familial hypercholesterolemia and lysosomal storage disorders, which result from errors in the signals or the transport machinery. And protein signals have become a crucial tool for researchers who genetically modify bacteria, plants, and animals to produce drugs. By adding a specific tag to the desired proteins, genetic engineers can, for instance, tag them for excretion, making them much easier to harvest.

But although Blobel's work is standard textbook knowledge these days, protein ZIP codes have seen rougher times. "People didn't like the idea of a signal [sequence] even as late as in the 1980s. Especially the proposed channel was a lightning rod for the opposition; some of them got very angry," Blobel says, adding that only when his team could show that the channel really existed did the tide turn for good. The idea was too obvious, says Rothman: "Often biologists think nature can't be that simple."

–MICHAEL HAGMANN

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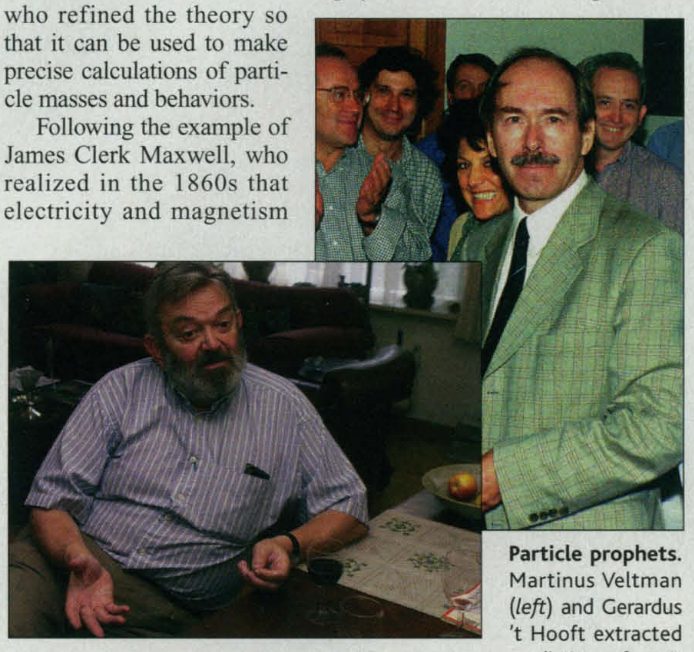
Theory Leads to Particles and Prize

In the world of subatomic particles and forces, a good map goes a long way. Electroweak theory, a key part of particle physicists' theoretical map, keeps leading them to new particles—and to Nobel prizes. The most recent of these, the 1999 Nobel Prize in Physics, was awarded last week to Gerardus 't Hooft and Martinus Veltman, two Dutch physicists who refined the theory so that it can be used to make precise calculations of particle masses and behaviors.

Following the example of James Clerk Maxwell, who realized in the 1860s that electricity and magnetism are aspects of a single electromagnetic force, physicists yoked together a second pair of forces in the 1960s to create electroweak theory. It unites electromagnetism with the weak force, which operates within the atomic nucleus and is responsible for certain kinds of radioactive decay. Electroweak theory predicted new force-carrying particles called W^+, W^-, and Z^0, but it was a frustrating tool at first. When used to calculate particle masses and behaviors, it tended to yield nonsensical answers—such as infinity.



Particle prophets. Martinus Veltman (*left*) and Gerardus 't Hooft extracted predictions of particle masses and behavior from electroweak theory.

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In 1969, Veltman, a professor at the University of Utrecht, and 't Hooft, then a doctoral student and now a professor at Utrecht, started working on a mathematical model that would make sense of electroweak interactions. By 1972 they had published the essentials of their method, which had an immediate and widespread effect on particle physics. "It was called a 'revolution,' " remembers Veltman, who is now an emeritus professor at the University of Michigan, Ann Arbor. "Things started falling in place."

Karel Gaemers, a particle physicist at the University of Amsterdam, says their main contribution to the field was the development of a technique for "renormalizing" the theory, which makes precise predictions for electroweak interactions possible. The technique does away with those pesky infinities, in part by replacing certain theoretical values with numbers determined by experiments. Veltman and 't Hooft also made many other refinements to the theory, based, for example, on unusual symmetries. Although the predictions their methods yield are not as precise as those of quantum electrodynamics—the theory that deals with electrons, positrons, photons, and their interactions—the electroweak theory comes quite close, says 't Hooft.

Renormalization allowed precise predictions of the masses of the W and Z particles, for example, which were ultimately created and detected in 1983 at CERN, the European particle physics laboratory in Geneva. It also pointed to an approximate figure for the mass of the top quark, years before it was discovered in 1995 at the Fermi National Laboratory near Chicago. "That was a great success of theory and experiment and calculational method—and 't Hooft and Veltman supplied the calculational method. … I think the prize was very well deserved," says physicist Steven Weinberg of the University of Texas, Austin, who himself shared a 1979 Nobel prize for developing the original electroweak theory.

Of all the particles predicted using 't Hooft and Veltman's methods, the only one still undetected is the infamously elusive Higgs particle. Physicists believe it ought to exist because without it in their equations, particles such as the W and Z should have no mass. Predicting its mass, however, is difficult: Although the particle interferes with many interactions, it does so only indirectly. 't Hooft and many other physicists hope that the Large Hadron Collider, expected to be completed by CERN in 2005, will capture this scarlet pimpernel of particles.

If the Higgs is found, its mass may rock the foundations of existing theories. Should the mass turn out to be much heavier than the current prediction—already a hefty 100 gigaelectronvolts—it will indicate the existence of a "new physics," says 't Hooft. "The situation will then become unpredictable. … We can expect new objects and unknown effects"—and a serious need for a new guide to the particle world.

–ALEXANDER HELLEMANS

Alexander Hellemans is a science writer in Naples, Italy.

A Winning Flash Dance

Ahmed Zewail can finish an experiment faster than you can bat an eye. Over the past 10 years, the Egyptian-born chemical physicist, who works at the California Institute of Technology in Pasadena, has pioneered the use of ultrashort laser pulses to witness the dance of atoms as they knit and break chemical bonds. Last week, Zewail's freeze-frame view of reactions won him the 1999 Nobel Prize in Chemistry.

At the molecular level, chemistry is breathlessly fast. Some reactions, such as the rusting of a nail, may seem sluggish, but that's because the individual molecules react only rarely. Once the reactants meet and hurdle an energy barrier, the making and breaking of bonds takes a mere 100 or so femtoseconds, or quadrillionths of a second. Before Zewail's work, few dreamed of ever seeing this speedy dance. Being able to do so, says University of Pennsylvania chemist

Earlier honors. Ahmed Zewail appears on Egyptian stamps.

Robin Hochstrasser, "caused a large number of chemists to think about chemical reactions in a different way, in real time."

The trick was coming up with an ultrafast camera capable of freezing the whir of molecules, much as a flash and a fast camera shutter can halt the blur of hummingbird wings in mid-flight. Fortunately for Zewail, in the late 1960s and 70s research groups around the world were developing lasers that generated shorter and shorter light pulses. A small tabletop device called a colliding pulsed mode-locked (CPM) laser—developed by Bell Labs researchers Charles Shank and Erich Ippen—proved to be the camera Zewail needed.

"We recognized that if we could get the time resolution shorter than a vibration of atoms in a molecule, we could see bonds breaking," says Zewail. The CPM laser and its successors generate a wide range of light frequencies and then emit them only during the brief moments when their wavelengths all march in lockstep, creating an intense pulse. The result is a flash as short as 7 femtoseconds, well within the time it takes the atoms in a molecule to vibrate back and forth.

To capture the action, Zewail constructed an apparatus to feed reactant gases into a vacuum chamber and then used a CPM laser as the equivalent of a camera and flash. He set up his laser to fire pairs of ultrashort light pulses. The initial pulse—the flash—supplies the energy that the target molecules need to surpass the energy barrier and begin reacting. The second pulse, fired mere femtoseconds later, illuminates the reacting molecules, which either absorb the pulse or respond to it by fluorescing at wavelengths that depend on their configuration. By varying the time interval between the two pulses and recording the absorbed or emitted light, Zewail can track the chemical reaction from the starting molecules, through the intermediate states that result as bonds are stretched, broken, and rearranged, to the final products.

In his first experiments, in the late 1980s, Zewail and his colleagues watched as molecules of iodocyanide split into their component ions in a reaction that took a mere 200 femtoseconds. "It was a wonderful set of experiments that had a big impact on chemistry," says Hochstrasser. By witnessing the birth and death of molecules in just femtoseconds, "we have reached the end of the road: no chemical reactions take place faster than this," noted the Royal Swedish Academy of Sciences in its award citation.

Zewail's work initially focused on simple reactions of gaseous molecules and answered basic questions about reaction mechanisms, revealing, for example, that molecules containing two equivalent bonds break them one at a time instead of simultaneously. Since then his group and others around the world have pushed the technology to chronicle chemical changes in liquids and solids as well. The result is a whole new discipline of femtosecond science, which has yielded insights into everything from how plants capture sunlight in photosynthesis to how the human eye manages to see at night when the light is faint.

This year's Nobel "was a wonderful choice and a well-deserved award," says Paul Corkum, who heads femtosecond science research at the National Research Council in Ottawa, Canada. For his part, Zewail says he has been "overwhelmed" by the response generated by the announcement. Thousands of congratulatory messages have poured in from Egypt alone, he says, including one broadcast on Egyptian television by the country's president, Hosni Mubarak. Zewail, whose portrait already appears on two Egyptian stamps, says such recognition by your native country "is an honor that lasts forever." Still, he says, it's not the same as recognition from scientific peers, epitomized by the Nobel prize: "You cannot match that." **–ROBERT F. SERVICE**

A Prize for Economic Foresight

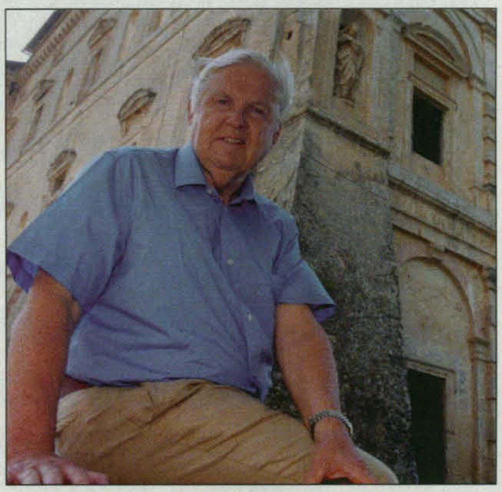
Robert Mundell did the work that won this year's Nobel Prize in Economic Sciences nearly 40 years ago. But evidence of what the Nobel prize committee called his "almost prophetic accuracy in terms of predicting the future development of international monetary arrangements" can be found today on every newspaper business page. Mundell's research, once considered esoteric and irrelevant, provides the framework for current understanding of international exchange rates and was used recently to establish the ground rules for the European Monetary Union.

The world was a very different place when Mundell received his Ph.D. from the Massachusetts Institute of Technology in 1956. "After World War I, most [international] capital systems collapsed," says Harvard University economist Ken Rogoff. From then until the early 1960s, a system of fixed exchange rates linked virtually all countries, and a mere trickle of funds passed between countries—compared to the estimated $2 trillion now exchanged on the international markets every day. "Capital flows were far less important," says Princeton University economist Peter Kenen, so economists tended to ignore exchange rates when analyzing domestic economies.

Perhaps it was his Canadian upbringing—Canada and the United States have always freely exchanged money—that made Mundell see things differently. Before his work, economists thought that governments could influence their domestic economies in two ways: by adjusting the money supply (monetary policy) or by changing spending priorities (fiscal policy). In papers written in the 1960s, when he was working at the International Monetary Fund, Mundell drew on Canada's experiments with both fixed and floating exchange rates to show how large capital flows limit governments' options.

He theorized that when international capital is highly mobile and the exchange rate is fixed, the central bank loses control of the money supply and hence of domestic interest rates; fiscal policy becomes the only tool left for influencing the domestic economy. As a result, says Rogoff, "we now know that fixed exchange rates are unstable" when capital flows increase. Market pressures inevitably force countries to adopt either floating exchange rates or a common currency.

The second possibility was, at the time, a startling one. In the late 1950s, currencies were almost synonymous with their parent countries. "The idea of France and Germany sharing a currency seemed very oddball at the time," says Rogoff. But in a watershed 1960 paper Mundell outlined the criteria under which multiple countries could successfully merge their currencies.



Worldly economist. Robert Mundell anticipated today's global economy.

His work influenced generations of economists. "Anyone with an economics Ph.D. was cheerfully force-fed his ideas," says Columbia University economist John McLaren. And they turned out to be dead on target. Throughout the 1990s, changes in the technology of trade and communication dramatically increased international capital flow and most Western countries abandoned fixed exchange rates. Even more surprising, eleven European states are well on their way to fully instituting a common currency following the principles Mundell set forth four decades earlier.

"He was far ahead of his time," says Kenen. Almost 40 years later, the framework Mundell developed "is still a workhorse of modern international macroeconomics." **–MARK SINCELL**

Mark Sincell is a science writer in Houston.

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