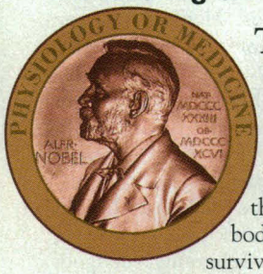
Eight Get the Call to Stockholm

This year's Nobel Prizes in science and economics were awarded for work on cell signaling, neutron scattering, organic chemistry, and game theory that has influenced decades of later research

Medicine: A Signal Award for Discovering G Proteins



The smooth running of virtually any community depends on good communications between individual members. And the same goes for the body, which could not survive without the intricate web of chemical signals—hormones, neurotransmitters, growth and differentiation factors—that coordinate the activities of its diverse populations of cells. No wonder then that the pathways that convey those signals to the cell interior have proved to be a fertile source of biological knowledge—and of Nobel Prizes. This year's prize for physiology or medicine is the latest in a string of awards going back several decades for discoveries that have helped decipher these pathways. It goes to pharmacologist Alfred Gilman of the University of Texas Southwestern Medical Center in Dallas and biochemist Martin Rodbell of the National Institute of Environmental Health Sciences in Research Triangle Park, North Carolina, for their discovery in the late 1960s and 1970s of key pathway molecules known as "G proteins."

The award had been expected for some time because researchers have found that these proteins, which help relay signals received at the cell membrane into its interior, affect an extremely wide range of biological activities (*Science*, 29 September 1989, p. 1446). "The rough number I give is that at least a third of signal transduction processes involve G proteins," says Lubert Stryer of Stanford University, who is himself an early pioneer of G protein research. For example, they are part of the pathways that enable cells to respond to hormones like epinephrine and glucagon, which help regulate fat and glucose metabolism, and to neurotransmitters such as acetylcholine. They are also part of the eye's light-sensing system as well as the odor-detecting system of the nose. Or as Gilman puts it, G proteins are involved in "everything from sex in yeast to cognition in humans."

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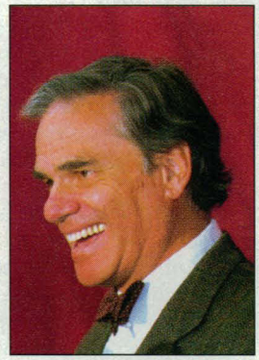
G protein isolator. And Alfred Gilman's group purified the first of the breed.

One indication of their importance, says another longtime worker in the field, Henry Bourne of the University of California, San Francisco, is that "some 50% to 60% of the drugs used in clinical medicine work on the receptors that talk to these G proteins." They include such widely prescribed medicines as the *beta*-blockers used to treat high blood pressure and heart arrhythmias. What's more, G protein malfunction contributes to serious human diseases, including cholera, whooping cough, and perhaps even cancer.

Both Rodbell and Gilman credit the late Earl Sutherland with providing the inspiration that started them on the path that led to their ground-breaking work. It was Sutherland, working with Theodore Rall in the 1950s at what was then Western Reserve University in Cleveland, who provided one of the first clues to how hormones transmit their signals to the cell interior.

Most hormones never enter cells themselves, but instead bind to specific receptors on the outer cell membrane, an event that sets in motion the chain of events leading to the appropriate cellular responses. Sutherland and Rall were trying to decipher how this binding kicks the cell into action. They provided part of the answer by showing that epinephrine exerts its effects by stimulating the production inside cells of a previously unknown compound called cyclic AMP (adenosine-3',5'-monophosphate). For the discovery of this first "second messenger," Sutherland received the 1971 medicine Nobel.

Still, Sutherland's work had not revealed just how the binding of epinephrine to its receptor might stimulate cyclic AMP formation. Enter Rodbell. In the late 1960s, while still at the main campus of the National Institutes of Health in Bethesda, Maryland, he decided to tackle the problem. At the time, researchers generally believed that adenylyl cyclase, the enzyme that synthesizes cyclic AMP, was an integral part of hormone receptors. But when Rodbell studied how hormones affect cyclic AMP production in isolated fat cells, he came to a different conclusion.



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Foundation layer. Martin Rodbell's work pointed to G proteins' existence.

He found that several hormones stimulate cyclic AMP production in the cells, and that they act through different receptors. As it seemed unlikely that all the receptors would have their own adenylyl cyclase activity, Rodbell proposed that the enzyme was a separate molecule in the cell membrane. When receptors are activated by binding to a hormone, Rodbell surmised, a third molecule, which he called a "transducer," links up with the adenylyl cyclase and initiates cyclic AMP synthesis. This idea, Rodbell recalls, "met with great resistance for a long time," partly because it ran counter to the accepted view of receptor action.

But in 1970, Rodbell, working with then postdoc Lutz Birnbaumer, uncovered a clue that would eventually help dispel the skepticism. The researchers found that glucagon, another hormone that stimulates cyclic AMP production, only exerts its effects if an energy-carrying compound called guanosine triphosphate (GTP) is present. Danny Cassel and Zvi Selinger at Hebrew University in Jerusalem also learned that the compound is broken down when epinephrine binds to its receptor. It seemed that some energy-consuming step lay in the signaling path. And that's where Gilman's work came in. Rodbell "laid the foundation," says Gilman. "He discovered that GTP was required, and we discovered why."

In the 1970s, Gilman, then at the University of Virginia School of Medicine in Charlottesville, set out to isolate the various membrane proteins needed to trigger cyclic AMP production in response to epinephrine. As one step toward that goal, Gilman lab member Elliott Ross wanted to see if he could restore adenylyl cyclase to membranes from a line of cells that apparently lacked the enzyme and were therefore unable to make cyclic AMP. He added a cell extract containing the enzyme to the membranes and got the expected result: They acquired the ability to

synthesize cyclic AMP when exposed to epinephrine. But he also found something quite unexpected: As a control, he used an extract that had been treated to inactivate adenylyl cyclase—yet membranes mixed with this extract also gained the ability to make cyclic AMP. It was this unexpected result that led to the isolation of the first G protein.

Ross and Gilman went on to show that the test cells in fact never lacked adenylyl cyclase; instead, they were missing Rodbell's transducer. This protein was present in the extracts they added to the cells, and that's what restored their cyclic AMP–synthesizing ability. The researchers also showed that the protein needs GTP for its action, a finding which led them to give it its name—G protein. But even though this biochemical information provided a helpful guide for the effort to isolate the protein, it took Paul Sternweis and John Northup of the Gilman group until 1980 to purify it.

It was a tough job because the protein is present in tiny amounts and the treatments used to remove it from membranes tend to destroy the activity of proteins. Indeed, says UCSF's Bourne, the work needed to identify and purify the first G protein "was an enormous test of skill. It was a real feat."

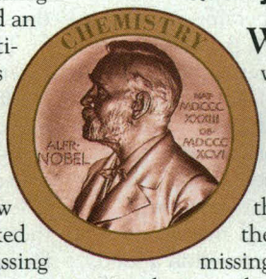
In the 14 years since Gilman's group isolated the first G protein, the field has exploded, aided partly by the newer gene-cloning technology that allows researchers to look for the corresponding genes rather than going through the tedious business of isolating the proteins themselves. Early on, researchers learned that the proteins have a modular structure, which helps explain why they have so many different properties and cellular roles. Each contains three kinds of polypeptide subunits, designated *alpha*, *beta*, and *gamma*, and so far, the newer gene analysis has picked up genes for 16 distinct *alpha* chains, five *beta* chains, and seven or eight *gamma* chains.

If the polypeptides produced by these genes could join up in all possible combinations, it would mean that there could be several hundred different G proteins. And that includes only the G proteins associated with membrane receptors. Gene studies have also revealed groups of proteins that have some structural similarities to G proteins, but work inside the cell. These include, for example, the protein product of the *ras* oncogene, whose mutations help cause several kinds of human cancers.

The long-anticipated award to Gilman and Rodbell for initiating this cascade of findings indicates that the signaling mechanisms within the scientific community are functioning well. Stockholm apparently got the message—and generated the appropriate response.

–Jean Marx

Chemistry: Snaring Elusive Quarry—And a Prize

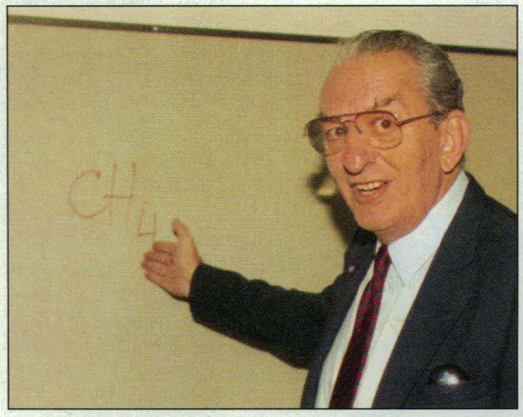


When organic chemists write out a reaction with reactants arrayed on one side and products on the other, they leave out an entire cast of characters that come and go during the reaction. True, these missing actors, called reactive intermediates, make only split-second appearances before vanishing again, but they exert a powerful influence over the way the reaction proceeds. In the 1960s, University of Southern California organic chemist George Olah found a way to snare these elusive compounds so that they could be studied. The work has paid off in basic research, in industrial processes—and this year, in a Nobel Prize for Olah.

By developing acids so strong that they could tame and stabilize these reactive intermediates, he opened the eyes of other chemists to a previously hidden universe, says California Institute of Technology chemist Jack Roberts. "These products have half-lives of millionths or hundred millionths of a second, or maybe even nanoseconds or picoseconds," he says. "If you can make something stable you can find out about the structure instead of just sitting around hypothesizing about it." Doing so took a leap of imagination characteristic of the Hungarian-born chemist, Roberts adds.

Olah says he became intrigued with short-lived organic intermediates even before he left his native Hungary and emigrated to the United States in 1957. At the time, these intermediate states were no more than hypothetical entities, postulated to explain how reactant molecules with a specific shape could metamorphose into products with a very different shape. Because chemists couldn't observe these intermediates directly, they had argued about their structure and behavior for 80 years, says Olah, and some even went so far as to question their existence. "It was a long-standing challenge. ... I was fortunate to have found a way to solve that puzzle."

The problem he had to overcome was that these intermediates, if they existed, would be so unstable that they would react almost instantly with anything they came into contact with. For one major class of intermediates, known as carbocations because they contain a carbon atom and carry a positive charge, the instability "goes back to acid-base chemistry," says Olah. Carbocations form in a large class of useful reactions in which an organic molecule reacts with a base. To force the reaction to take place, chemists add an acid catalyst, which briefly lends an extra positively charged hydrogen to the organic molecule, turning it into a very unstable and reactive acid. This intermediate tends to react with almost anything by giving up this hydrogen ion or by stealing electrons.



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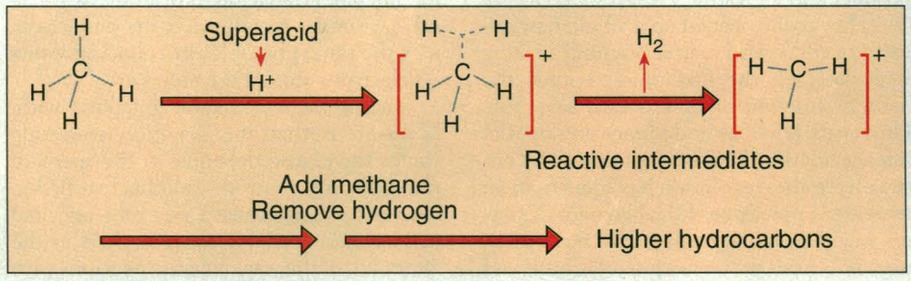
Carbocation in the bag. Chemistry nobelist George Olah.

"We needed to create conditions where we could observe these very reactive organic acids," says Olah, and his strategy was to fight fire with fire. He knew that when compounds such as antimony pentafluoride are dissolved in water, the result is a "superacid" thousands of times stronger than traditional strong acids, such as hydrochloric acid. Superacids are so potent because the hydrogen ion is paired with a complex negative ion containing an electron-hungry metal. The electron shortage makes the acid unusually eager to donate the positive hydrogen ion to other molecules—or to steal electrons from them.

And Olah found that by beating carbocations at their own game, superacids could prevent carbocations from reacting, stabilizing them for months on end—long enough



SOURCE: SURYA PRAKASH/USC

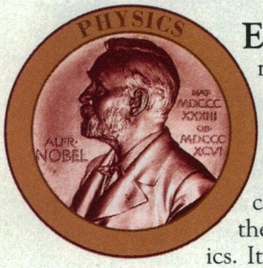
Steadying influence. By stabilizing an intermediate, a superacid opens the way to complex products.

for him to study their structure with nuclear magnetic resonance (NMR) and other techniques. Among the early results of this strategy was Olah's discovery that some of these intermediates looked nothing like the carbon-centered ions familiar to chemists: Instead of the usual tetrahedral shape, they were pentahedral or even hexahedral.

Since then, Olah and other chemists have developed a whole family of new superacids that have made their mark in industry as well as basic research. By stabilizing reactive intermediates, for example, these acids can induce or regulate industrially important reactions, such as those involved in synthesizing high-octane gasoline. Other chemists are delighted that Stockholm has now acknowledged this revolution. "It is wonderful to see this field of reactive intermediates being recognized," says Caltech chemist Peter Dervan, "and if you had to pick a pioneer it would be Olah."

–Faye Flam

Physics: Neutron Cartographers Lauded for Mapping Materials



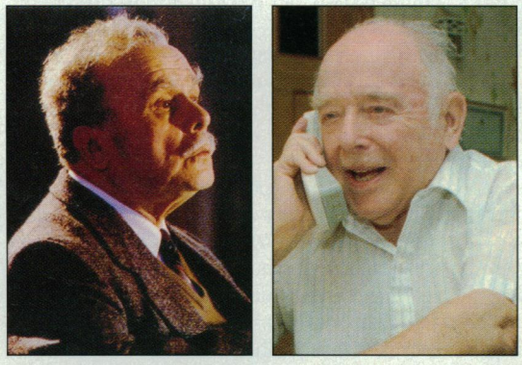
Explorers of unknown realms used to be rewarded with land, titles, and money. This year a scientific journey into terra incognita was awarded the Nobel Prize in physics. It went to a pair of researchers who developed ways to use beams of neutrons—uncharged subatomic particles—to chart the hidden atomic structure and behavior of matter.

Clifford Shull of the Massachusetts Institute of Technology earned his half of the award for developing a technique called neutron diffraction to determine the location of atoms in a sample of material. The other laureate, Bertram Brockhouse of McMaster University in Hamilton, Ontario, was honored for his work on neutron spectroscopy, which shows how these atoms move. Developed more than 40 years ago, the neutron probes are widely used today to investigate the fundamental properties of materials in such widely differing fields as high temperature superconductivity, magnetism, and polymer and viral structures.

"They really opened up a whole new domain of condensed matter physics," making it possible for the first time to study the atomic structure of bulk solids, says Yale University physicist and former presidential science adviser D. Allan Bromley. "The entire electronics revolution has come from an increased knowledge of the behavior of matter made possible in part by these techniques." And the selection of Shull and Brockhouse for the prize is "a natural pairing," says John Axe, a neutron scattering researcher and associate director of the Brookhaven National Laboratory on Long Island, New York; although the two Nobelists never collaborated, their work was extremely complementary.

Both Shull, age 79, and Brockhouse, age 76, began their explorations into the use of neutron beams shortly after World War II. Earlier, in the 1930s, physicists such as Enrico Fermi had suggested that neutrons should be able to probe deep within a solid, because their lack of charge kept them from interacting with the electrons in that solid. Neutrons diffract not off an atom's electrons, but its nuclei. Shull, who joined a research team in 1946 at Oak Ridge National Laboratory headed by the late Ernest Wollan, was working on a way to use the pattern of defracted neutrons to identify how particular atoms were arranged in solids.

The key to determining these arrangements was the understanding borrowed from quantum mechanics that neutrons—like other subatomic constituents—behave not only as particles, but as waves. When neutrons interact with atoms in a crystal, they produce "scattering waves" that move out from the crystal. These waves then interact—either reinforcing each other if they are in phase or canceling each other when they are out of phase—to produce a unique scattering pattern. And because the direction these waves travel depends in part on the relationship of atoms in a solid, the scattering pattern created by neutrons is different for different arrangements of atoms in a crystal. (A similar technique, x-ray diffraction, uses the same principles in bouncing x-rays off electrons around the atoms.)



Prize-winning material. Bertram Brockhouse *(left)* and Clifford Shull pioneered ways of using beams of neutrons to explore the nature of matter.

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The problem Shull was grappling with, however, is that the direction scattering waves travel also depends on the speed of the incoming neutron—and nuclear fission reactors, which produce neutrons and had just become available to researchers in the aftermath of the war, generate neutrons with a variety of speeds. So Shull and his colleagues set out to produce a "monochromatic" beam of neutrons, all of which had the same velocity.

Their solution was to pass beams of these diversely energized neutrons through crystals of different materials, such as sodium chloride. Like prisms that separate light into different wavelengths, atoms in these crystals deflect neutrons with different energies in different directions. The researchers could then isolate one beam of neutrons with uniform energies and use it as a probe to produce the structure-revealing diffraction pattern in their test sample.

Shull and his colleagues also developed a similar neutron scattering technique to probe the arrangement of magnetic atoms in a sample. "That was a big deal because it opened the door to studying magnets on an atomic level," says Axe. These studies have been vital in the development of everything from efficient magnets in motors to magnetic information storage.

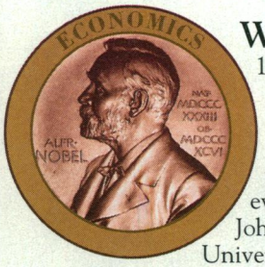
Shortly after Shull started developing these diffraction techniques, Brockhouse joined the staff of the Chalk River research reactor in Canada and began exploring how atoms in a sample move. Thermal energy causes atoms in crystals to vibrate, and the vibrations of one atom prompt neighboring atoms in the crystal lattice to resonate. Because the atomic makeup of different crystals is unique, each has its own characteristic vibration pattern. A crystal's vibrational energy, measured in units called phonons, along with its electronic characteristics, shapes its ability to conduct heat or electricity.

Brockhouse used neutrons to measure that energy. As neutrons pass through the lattice they either give up or pick up energy from it, thereby changing their own speed. Brockhouse measured the vibrational energy of crystal lattices by comparing the speed of neutrons entering and emerging from samples. He started with a monochromatic beam of neutrons, produced by an apparatus similar to Shull's, and passed the beam through his test sample. The neutrons emerged moving at a range of different speeds. To identify their speed—and therefore how much energy they had lost or gained—he simply diffracted them through another crystal, which diffracted them in different directions according to their velocity.

"Much of the theory of diffraction and lattice vibrations was there," says Brockhouse of his early work. "It just hadn't been brought together. And I just realized that it could be done with the current technology." And with the physics Nobel, the two scientists, always complementary but not collaborative, have been brought together as well.

–Robert F. Service

Economics: Game Theory's Winning Hands



When the names of the 1994 Nobel laureates in economics were announced last week, they had a familiar ring to—of all people—evolutionary biologists. John Nash of Princeton University, John Harsanyi of the University of California, Berkeley, and Reinhard Selten of the University of Bonn will split the award for their work in turning game theory into an indispensable tool for analyzing economic competition. But, in a rare crossover between economics and the natural sciences, many of the ideas and mathematical techniques they pioneered are at the cutting edge in understanding competition within and among biological species.

"The Nash equilibrium turns out to be terribly important in biology," says Peter Hammerstein at the Max Planck Institute for Animal Behavior Research in Seewiesen, Germany. "And last week [at an international conference] I spent a lot of time explaining to a group of biologists why Selten's idea of 'subgame perfection' is important to them." Such concepts are proving vital in analyzing a range of biological data, from sex ratios to animals' decisions about whether to fight each other for territory or food.

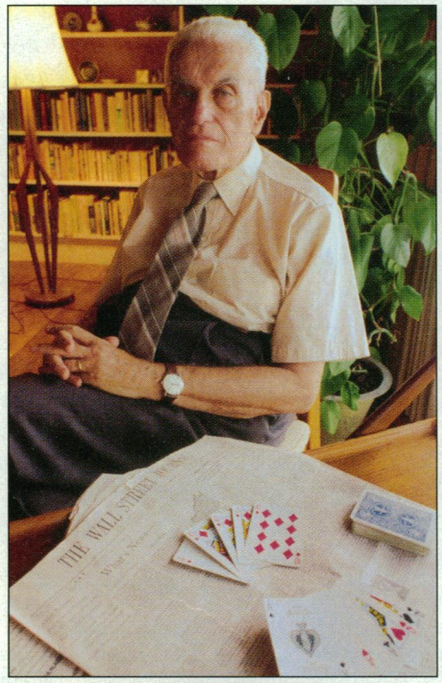
Both the economic and the biological techniques are based on the mathematical study of competitions between two or more players. Whether the game is poker, chess, or selling automobiles, players must take their competitors' likely responses into account when deciding on their own actions. Such competitions become a series of thrusts and counterthrusts aimed at gaining an advantage—or at least avoiding a disadvantage.

Traditionally, economic theory took a very different tack. In standard supply-and-demand analysis, economists assume there are so many players that the action of any single competitor has only a negligible effect on the market as a whole. This is a good approximation for such things as the housing market, with its numerous buyers and sellers, but it falters in many other areas where two or three companies dominate.

In 1944 the mathematician John von Neumann teamed with economist Oskar Morgenstern to show how game theory could help. Their book, *Theory of Games and Economic Behavior*, analyzed a variety of economic systems with game-theoretic tools. They looked, for example, at two-person zero-sum games, in which one person's gains are the other's losses, and showed that under certain conditions there is always an "optimal" solution—that is, a situation in which neither player can improve his or her outcome by unilaterally changing strategy.

Nash greatly extended this work in 1950 by generalizing two-person zero-sum games to many players with various goals. He introduced the idea of a "Nash equilibrium"—a situation in a multiplayer game in which each player's position is optimized with respect to the others'. Economists now believe that many stable points in the economy—such as the fixed prices the Post Office and Federal Express charge for overnight mail—are better thought of as Nash equilibria than as products of supply and demand forces.

But the Nash equilibrium assumes that each player is perfectly informed about the others' intentions—a condition rarely met in practice. In the late 1960s Harsanyi analyzed what happens in games where the players don't have complete information—as in the U.S. banking system. Banks must determine their interest-setting strategies without knowing just how the Federal Reserve Board will fix its own interest rates in response to inflation and unemployment.



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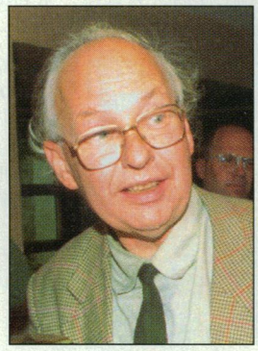

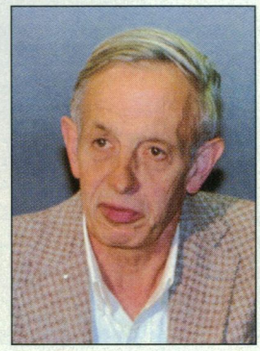

Masters of the game. Economics nobelists John Harsanyi *(top)*, Reinhard Selten *(left)*, and John Nash.

And Selten has sharpened the idea of an equilibrium point to eliminate some of the economically unreasonable situations that qualify as Nash equilibria. In theory, for example, a monopoly sustained because the dominant company threatens any start-up competitor with a price war is a Nash equilibrium—even if the threat is hollow because the company could not afford to wage a price war. In 1965 Selten showed how to cut out such solutions when he introduced the idea of "subgame perfection," a refinement that insists players act rationally in all situations, even those that could not have been reached through completely rational actions.

Even as these ideas were spreading through economics, they were jumping disciplinary lines into biology. The trigger was a 1973 paper by John Maynard Smith of the University of Sussex in which he used game theory to analyze evolutionary competition and independently came up with a concept much like the Nash equilibrium. He showed that a species will tend to adopt an "evolutionarily stable strategy" (ESS). Once a population reaches an ESS, any mutation appearing in a small percentage of the population will die out because its bearers will be at a disadvantage relative to the whole group. In the past two decades, Maynard Smith says, biologists have shown that ESSs explain the persistence of many adaptations, including the nearly universal male-female ratio of about 50–50.

In a more direct borrowing from economics, a few evolutionary biologists have put Selten's idea of subgame perfection to work in analyzing such things as parental investment in child-raising and why some animals desert their mates. And Selten himself has made contributions to evolutionary biology. He and Hammerstein, for instance, have analyzed animals' fighting behavior in "asymmetric conflicts"—conflicts in which competitors face different odds and seek different gains.

Ironically, given that it is the economics work that garnered the Nobel Prize, evolutionary game theory is the more successful version in at least one sense, notes population biologist Martin Nowak of Oxford University. It can be difficult to test economic models precisely because the payoffs sought by the players aren't always obvious. It's hard to know, for instance, if a company is primarily seeking profit or long-term growth or simply wants to crush its competition. But in evolution the models can often be tested, Nowak says, because "there's a clear concept of what a payoff is." If a player survives and has many children, its strategy was a winner. Otherwise the game was a bust.

–Robert Pool