NOBEL PRIZES

U.S. Researchers Gather A Bumper Crop of Laurels

Colleagues of this year's Nobelists were pleased but not surprised by the news from Stockholm last week; all of the recipients had made seminal contributions to their fields. Perhaps the only surprise was the overall pattern: Four of the five winners of the $1.2 million prizes did their Nobel Prize–winning research in the United States, a sharp turnaround from last year's domination by European researchers.

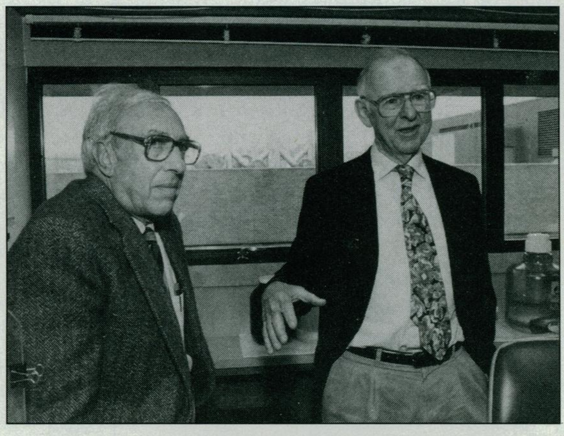
NOBEL MEDAL: THE IMAGE BANK

Medicine: A Signal Contribution to Cell Biology

Not many biochemical reactions could have bred three separate Nobel Prizes. But one relatively simple reaction has proved rich enough to do so: the breakdown of glycogen, the body's principal energy-storage compound, into the sugar glucose. "I always said that glycogen metabolism revealed innumerable biological principles," asserts biochemist Edwin Krebs of the University of Washington School of Medicine in Seattle. And he should know. With his long-time Seattle colleague, Edmond Fischer, Krebs has just been awarded the 1992 Nobel Prize for Physiology or Medicine, the latest in the series of Nobels going back to the 1940s won by researchers who have studied glycogen metabolism.

The principle revealed by Fischer and Krebs' work now infuses virtually all aspects of cell biology research. In experiments done nearly 40 years ago, the two biochemists showed for the first time that the activity of an enzyme—in this case the glycogen-splitting enzyme called phosphorylase—can be turned on and off by the reversible addition of a phosphate group to the enzyme protein. "At that time, we had no idea whether it was a unique reaction, or maybe only limited to carbohydrate metabolism," says Fischer. "But as luck would have it, [reversible phosphate addition] is one of the most prevalent mechanisms by which you can turn on or off a reaction."

Indeed, since Fischer and Krebs did their ground-breaking work, such reversible phosphate additions (known technically as phosphorylation reactions) have been shown to control the activities of hundreds of enzymes, regulating everything from hormonal responses to muscle contraction, immune responses, and cell growth and division. The importance of the control exerted by these phosphorylation reactions can be seen from what happens when they go awry. If this happens in the cell's growth control pathways, for example, it may lead to the run-away cell growth of tumors. As Joan Brugge of Ariad Pharmaceuticals in Cambridge, Massachusetts, one of the many researchers following in Fischer and Krebs' footsteps, puts it, the Nobel-winning work "has initiated a whole field of research that concerns signaling processes that control cellular events that are central to human life and death."



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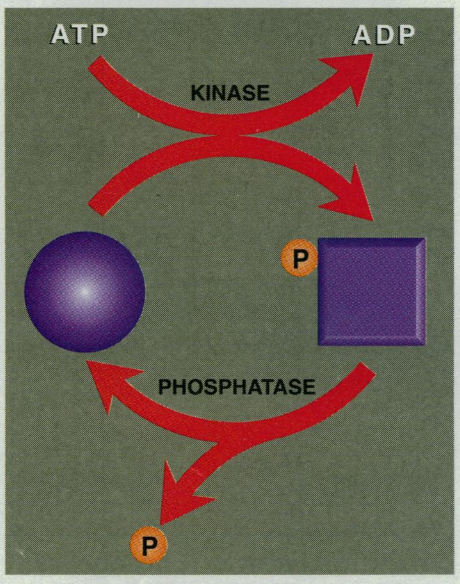


HILLARY RADBILL

Turning on and off. Medicine winners Edmond Fischer *(left)* and Edwin Krebs showed how phosphate addition and removal control enzyme activity.

Krebs' path to the Nobel Prize began, he says, in the late 1940s, when he was working on the phosphorylase enzyme from muscle in the lab of biochemists Carl and Gerti Cori at Washington University School of Medicine in St. Louis. The Coris had won the first of the glycogen-related Nobels in 1947 for work that included the discovery and isolation of the enzyme, and they had shown that it exists in both active and inactive forms. They did not, however, pin down the difference between the two forms.

That was the puzzle that led Krebs to join forces with Fischer, who had gained experience with phosphorylase while working with a plant version of the enzyme at the University of Geneva, Switzerland. In 1953, the researchers began collaborating at the University of Washington. They soon showed that the inactive enzyme is converted to the active form by addition of a phosphate, which is transferred to the protein from the high-energy compound adenosine triphosphate (ATP). Removal of the phosphate, they found, turns the phosphorylase off again.

Since the phosphate addition and removal, like all other biochemical reactions in the cell, had to be carried out by enzymes, the next step was to find the responsible enzymes. Fischer and Krebs went on to isolate the first protein "kinase," the name given to enzymes that transfer phosphate from ATP to proteins. They also found the enzyme, called a phosphatase, that removes the phosphate.

That still left the question of what stimulates the kinase to turn on glycogen breakdown in the first place. An answer lay in the intersection of Krebs and Fischers' work with a line of research being pursued by Earl Sutherland, another alumnus of the Cori lab. Sutherland, too, had picked up on the fact that reversible phosphorylation controlled the activity of the phosphorylase enzyme. After that, however, Sutherland's research went in a different direction.

The initial stimulus to glycogen breakdown, researchers knew, comes from hormones such as epinephrine, which releases glucose to provide the energy for an animal's "fight or flight" responses in times of stress. Sutherland showed that epinephrine exerts its effects by stimulating phosphorylase activation. But epinephrine doesn't stimulate the enzyme directly, Sutherland found. Instead it works by increasing the production within cells of another biochemical called cyclic AMP.

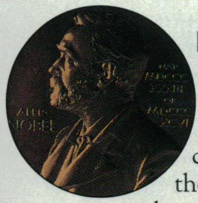
For his discovery of cyclic AMP, which came to be known as a "second messenger" (the hormone is the first), Sutherland won the second of the phosphorylase-related Nobel Prizes in 1971. He didn't show exactly how cyclic AMP stimulates phosphorylase, however, and that's where Krebs and Fischers' discovery of the protein kinases comes in. Krebs found that cyclic AMP stimulates the kinase that phosphorylates, and consequently activates, phosphorylase.

Krebs and Fischer's kinase subsequently turned out to be the linchpin in cellular responses to other hormones, such as the secretion of adrenal gland hormones triggered by adrenocorticotrophic hormone and the triglyceride fat breakdown stimulated by glucagon. And it's far from the only kinase enzyme identified since then. The Nobel Academy's statement on the medicine prize says: "We now estimate that perhaps 1% of the genes in the entire genome encode protein kinases. These kinases regulate the function of a large proportion of the thousands of proteins in a cell." But if one area in particular has blossomed in recent years, it's studies of the role of the protein kinases and phosphatases in growth control.

Roughly half of the cancer-causing oncogenes, for example, are now known to encode protein kinases. These are mutated forms of enzymes that occur normally in the cell's growth control pathways but in their oncogenic forms contribute to tumor development. Phosphatases, too, may participate in growth control, possibly counteracting the kinases' effects by removing phosphates from key proteins in the pathways. Just a few years ago, for example, Fischer's group played a major role in identifying a new class of phosphatases that may help regulate cell growth (*Science*, 15 February 1991, p. 744).

In talking to *Science*, both Krebs and Fischer expressed surprise that they were awarded this year's medicine prize. "So much superb work has been carried out by so many investigators," Fischer says, "you wonder why we were selected." But their colleagues have no trouble at all with the idea. "It's a wonderful prize," says Josef Schlessinger of New York University Medical Center, whose own work focuses on the role of kinases and phosphatases in cell growth. "It's a prize that should have been given earlier." Another kinase expert, Tony Hunter of the Salk Institute in La Jolla, concurs: "We are all pleased that they have finally been recognized."

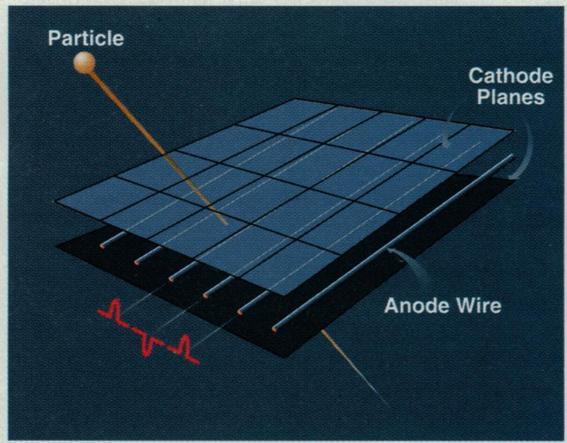
–Jean Marx



Physics: Applause for a High Wire Act

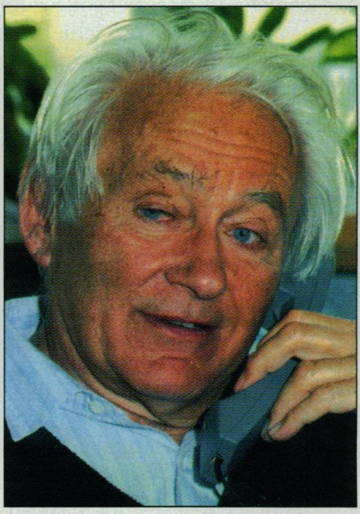
When high-energy physicists search for a new particle, they can't capture it in a test tube or pin it on a microscope stage. Instead, they have to watch for a fleeting signal of their quarry: the fireworks of decay particles it releases after briefly materializing in a high-energy collision. That requires a quick eye as well as a sharp one, because physicists may have to track billions of collisions, as particles smash into each other thousands of times a second in an accelerator, to find the precise signal they want. Now, acknowledging just how much particle physics owes to the availability of such a sharp, quick eye, the Swedish Academy has awarded this year's physics prize to the French researcher who made the key development: Georges Charpak of CERN.

In work done at CERN in 1968, Charpak devised the "proportional wire chamber," which not only tracks the paths and energies of the charged particles that spray out from a high-energy collision, but does so thousands of times faster than most previous methods. Since then, his chamber has become a standard item in particle detectors—so much so, says experimental physicist Tom Kirk of the Superconducting Super Collider (SSC) Laboratory in Waxahachie, Texas, that "practically every experiment in high-energy physics uses a version of it." Charpak's wire chamber helped physicists snare two prize quarries during the 1970s and '80s: the charm quark and the W and Z particles, both of which have already earned Nobel Prizes for their discoverers. And if more particles are waiting to be discovered in the next generation of accelerators, the SSC and CERN's Large Hadron Collider, they'll likely be detected by variants of Charpak's original invention.



HILLARY RADBILL

Caught midflight. A charged particle speeding through Georges Charpak's wire chamber deposits a negative pulse, bracketed by positive pulses in neighboring wires.


AP/WIDE WORLD PHOTOS

At the time he developed it, physicists trying to trace the particles spawned in their machines often did so by studying photographs taken in bubble chambers—tanks full of superheated liquid hydrogen, which forms a telltale trail of bubbles wherever a particle streaks through. But because such photographs could be taken only every second or so, they couldn't keep pace with improved accelerators, and analyzing them to learn the types of particles and their energies was slow and laborious. "The pictures were a bottleneck," Charpak recalls.

By replacing the bubble chamber and camera with a gas-filled chamber containing a network of closely spaced charged wires linked to amplifiers and recorders, Charpak eliminated the bottleneck. Because the chamber makes an electronic record of each passing particle, it's much faster than the mechanical eye of the camera, explains Fermilab detector physicist Vladimir Peskov, who worked with Charpak at CERN. And the records are much easier to interpret than a photograph. "The chamber gives you the answer immediately, in the form of electronic signals," says Peskov.

As a charged particle speeds through the chamber, it ionizes atoms of gas, freeing electrons that drift toward the nearest charged wire. There the electrons trigger a signal—and at the same time induce electrical pulses of opposite sign in adjacent wires, making it easy to pin down just where the particle had passed. Since the chamber includes many criss-crossing layers of wires, the set of wires tripped by each particle gives a three-dimensional record of its path. Simple, yes, says Kirk. But "like all great inventions, you ask, 'Why didn't I think of this?'"

Charpak himself says he was surprised by how quickly other physicists adopted it. But Peskov notes that, in retrospect, the time was right for the invention to take the field by storm. Particle accelerators were being scaled up to produce far more collisions than ever before, and "electronics were at the right level" to compile and analyze the signals rapidly. Detector designers quickly began combining wire chambers with other sensors, such as calorimeters, into the giant detectors that have become the hallmark of high-energy physics.

Hastening the spread of the new technology was the constant stream of improvements coming from Charpak's detector development group at CERN and from other physicists intrigued with the new device. One offshoot of the original device was the so-called drift chamber. The spatial precision of the original chamber was limited to a few millimeters, the spacing of the wires. But Charpak realized he could sharpen that resolution by taking into account the known rate at which electrons set free by each particle drift toward the nearest wire. The insight led to the drift chamber, which analyzes the time delays between the event that spawned the particle and the pulses recorded by the wires to give an even sharper picture of the particle's path.

Having weaned physics from its dependence on photographic film, Charpak is now trying to do the same thing in biology. Open any biology journal, says Charpak, and "you see all these ugly pictures obtained with film. Why? Because we physicists haven't given biologists a detector that can localize electrons." To make amends, Charpak is now adapting his wire chambers to record the particles emitted by radioactively labeled gels and tissues, yielding faster, sharper, and—to Charpak—prettier pictures than a film can.

Meanwhile, Charpak's colleagues in physics, recalling his earlier achievements, are reacting to the news of his prize with a sense of the inevitable. Says Kirk, "All of us were waiting for this to happen."

–Tim Appenzeller

Chemistry: A Winning Electronic Two-Step

Rudolph A. Marcus was at an electrochemistry conference, listening to a talk in a Toronto hotel lecture hall, when a meeting official informed him that he had an urgent phone call. "I was worried," Marcus recalls, wondering if it was bad news. Not by a googol of electrons, it turned out. A delegate of the Royal Swedish Academy of Sciences was waiting for him on the other end of the line. The news? Marcus, a Canadian-American chemist who has been at the California Institute of Technology since 1978, had just become this year's Nobel laureate in chemistry.

As the basis for the award, the academy cited "his contributions to the theory of electron transfer reactions in chemical systems." These reactions, in which at least one electron passes between atomic or molecular reaction partners (or from one part of a molecule to another), pervade the living and nonliving realms. The light of fireflies, photosynthesis in leaves, and the energy-generating processes of every living cell all hinge on reactions in which electrons are handed off from one molecule to another like hot potatoes, altering chemical personalities as they go. Technology also makes use of electron transfer reactions—they generate current in batteries and deposit the thin plating of silver on dinnerware. And the corrosion that attacks human creations is an electron transfer process as well. "It is one of the central kinds of reactions of all chemical and biological systems," says chemist Brian Hoffman of Northwestern University, whose own work focuses on how electrons transfer between proteins nestled next to each other. "Rudy, in large part, provided us with the conceptual tools to think about it."

Marcus did so in a series of now classic theoretical papers published between 1956 and 1965, mostly when he was at the Polytechnic Institute of Brooklyn. The concepts and equations Marcus developed, and has since expanded and refined, go by the rubric of Marcus Theory. He has been known to present the theory to students without revealing its name, however. The theory rigorously describes how subtle changes in the geometric arrangement of atoms in the molecules of a reaction, or in the surrounding medium, can affect the height of the energy barrier that electrons must overcome before transferring from one reactant molecule to another. Equipped with Marcus' theoretical framework, scientists can predict whether a charge-transfer reaction will progress, and how fast—an ability central to applied pursuits such as designing batteries and biosensors and to fundamental ones such as understanding photosynthesis and cellular metabolism.

To other chemists, the wide-ranging impact of Marcus' work has put him in the running for the prize for years. "Some of us think this is overdue," says Marcus' Caltech chemistry colleague Harry Gray, an electron transfer research aficionado in his own right. "He has been the major force in this field from the theoretical point of view," says Gray. Even Marcus allows that underneath the shock of hearing that he actually had won the most prestigious science prize in the world, the news wasn't entirely unexpected. That doesn't just reflect an honest appraisal of his own work, however; each year, rumors ripple through the small world of Nobel hopefuls almost as fast as electrons ripple through chemical systems. "I knew I had been nominated," Marcus says.

The award may have kept him away from some of the electrochemistry talks in Toronto, but it isn't going to interfere with his current work: overseeing a team of seven graduates and research associates at his Caltech lab who are delving into new aspects of electron transfer. A current focus, says Marcus, is on reactions in which electron transfer occurs over distances of a billionth of a meter or so—quite long in the molecular world—in cytochrome C and other proteins important in photosynthesis and cellular respiration. Such studies should reveal how energy flows through these large molecules and perhaps point toward possible spinoffs, such as improved devices for tapping solar energy.

Hoffman, for one, isn't surprised that after almost 40 years, the topic hasn't lost its grip on Marcus. "What could be simpler than one electron going from here to there?" Hoffman queries. And then again, "What could be more complicated?"

–Ivan Amato

AP/WIDE WORLD PHOTOS

Winning smile. Chemistry laureate Rudolph Marcus after getting the call.

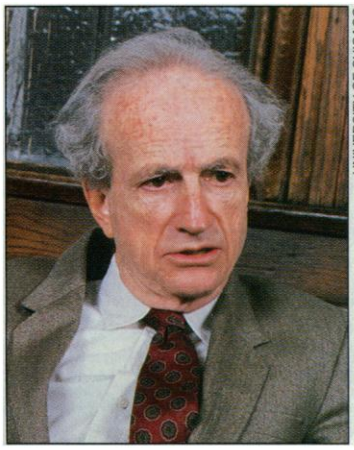
Economics: Bringing It All Home

Many Nobelists win their honors by leading their disciplines into unknown realms—the intricate signaling pathways of the living cell, for example, or the submicroscopic structure of matter. In the work recognized by this year's Nobel Prize in economics, University of Chicago economist Gary Becker did just the opposite. He brought the abstruse science of economics to bear on the most familiar of concerns: marriage, child rearing, crime, and discrimination. For 40 years, while other economists deployed their mathematical tools in fields such as industry and agriculture, Becker was bringing economics home.

But though the issues he studies may seem mundane, Becker's effort to add them to the fold of economics was once regarded as revolutionary. When he began his work, many traditional economists thought he was sullying the field, and the sociologists, anthropologists, and population biologists whose domain was family issues looked on Becker as an ill-informed interloper. By now, however, after an impressive series of essays and books, not just economists but also political scientists and sociologists have taken up Becker's methods. Says fellow Chicago economist James Heckman, "Becker not only stimulated people to look at things that were considered off-limits, but he also organized thinking for looking at these issues."

The premise underlying Becker's research is that rational economic choices govern most human behavior, not just the grand purchasing and investment decisions traditionally studied by economists. A household, Becker proposed, is a kind of factory: It takes materials—bundles of purchases from the shopping center—and converts them into goods and services such as meals, shelter, and entertainment. Education and income, he found, all affect how much time members of the household devote to their work in this factory, and how much "capital"—labor-saving goods, child care, and prepared foods—they substitute for labor.

That kind of analysis has led to insights that predicted many social trends. In the 1950s, for example, well before the civil rights movement emerged, Becker probed discrimination in the workplace and concluded that it was costly to both the perpetrator and the victim. In his economic analysis of families, he recognized that the "no fault" divorce laws being passed in the 1970s would boost the number of poor, single-parent families headed by women. And his early studies of "human capital" led him to conclude that as families' income rose, they would tend to have fewer children and invest more in their education.



UNIVERSITY OF CHICAGO

Home economist. Gary Becker makes three in a row for Chicago.

But just in case his status as iconoclast starts to pale, Becker has recently been studying the incentives and disincentives that lead to criminal behavior. Simply asking, When does crime pay? has led him to some unsettling conclusions. He has noted that the probability of getting caught is a much greater deterrent to crime than the severity of punishment; when laws are not well-enforced, he finds that criminal behavior is indeed the rational choice. His analysis has also convinced him that the social and legal costs of enforcing some drug laws impede efforts to curb more serious crimes.

Becker believes that the conclusions uncovered by such work should play a stronger role in public policy; indeed, he has argued for the legalization of some milder drugs, such as marijuana. But according to his students and colleagues, he is not flamboyant. Instead he commands respect with a gentle, probing manner. During lectures, says Heckman, Becker often uses the Socratic method to draw students into discussions. "His is a very penetrating curiosity," Heckman adds, "and everyone who enters his class, including fellow faculty members, is engaged."

One key to Becker's success may be his unwillingness to accept limits to that probing. Speaking fancifully, a colleague notes, "He has the intellectual rigor to make a formal model of the economics of Jewish guilt... [and] that is to his credit." Indeed, his colleagues say the only surprise in Becker's award is that, having awarded the 1990 and 1991 prizes to two Chicago economists, Merton Miller and Ronald Coase, the Swedish Academy would choose this particular year to honor him.

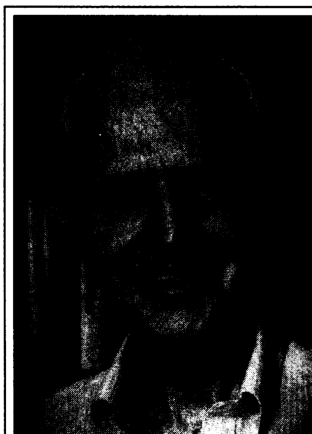
–Anne Simon Moffat

Biology: There's Honor Outside Stockholm

The Swedish Academy of Sciences doesn't hold a monopoly on prestigious science awards. Almost a decade ago, in honor of the late Emperor Hirohito (Showa), Japan established the International Prize for Biology, meant to recognize areas of research the Nobel Prize in Medicine or Physiology might not cover. This year's prize, carrying a $80,000 check and a trip to Japan for a formal ceremony before the country's highest officials, goes to Knut Schmidt-Nielsen, a Duke University physiologist, for his lifetime of pioneering work on how animals adapt to their often extreme environments.

While the molecular biologists and high-energy physicists who populate the ranks of Nobelists seek unifying principles, Schmidt-Nielsen's work has focused on diversity. His experimental subjects have ranged from kangaroo rats to camels to seagulls. "He has this remarkable ability to look at animals and intuitively figure out how they work," says physiologist Henry Prange of Indiana University, a former student of Schmidt-Nielsen's.

Schmidt-Nielsen sums up his method succinctly: "I only ask simple questions." One of the first was a question familiar to schoolchildren: How do some animals go without drinking? As Schmidt-Nielsen quickly adds, such questions may not have simple answers; this one took him to the Arizona desert for several years in the late 1940s to examine the water metabolism of rodents like the kangaroo rat. "It was unthinkable that mammals could live without free water when we began the kangaroo rat work," he recalls. But a close look at the animal's diet, lifestyle, and physiology showed the rat does just that by becoming a miser with its own internal water supply. To avoid the drying desert heat, the rodent emerges from its burrows only on cool nights. More important, Schmidt-Nielsen found that the animal conserves water by excreting highly concentrated urine and cooling the air it exhales to capture water vapor.



JIM WALLACE/ DUKE UNIVERSITY

A focus on diversity. Physiologist Knut Schmidt-Nielsen.

Later, in the 1950s, Schmidt-Nielsen studied how sea birds cope with the converse challenge: lots of water, but none of it fit to drink. He devised an experiment in which he would give a bird a dose of seawater and monitor the salt content of its excreta. But almost immediately after the bird drank up, Schmidt-Nielsen noticed a few drops of water around the bird's beak. A quick test showed the liquid had a high concentration of salt. In a flash, he deduced the existence of salt-secreting glands near the bird's eye. The glands turned out to be standard equipment in marine birds and reptiles, allowing them to get rid of unwanted salt.

In the decades that followed, Schmidt-Nielsen hopped from animal to animal and topic to topic, making findings that solved physiological mysteries and launched new areas of study. "He makes the important discoveries and moves on," says physiologist Don Jackson of Brown University. For example, Schmidt-Nielsen has been a pioneer in the area of "scaling," the study of how body size affects an animal's life. He was also among the first to document the features of the avian respiratory system that allow birds to extract oxygen efficiently at low atmospheric pressures, an obvious benefit for flying creatures.

Besides admiring his scientific legacy, Schmidt-Nielsen's colleagues also applaud his ability to popularize his field and engage students. His textbooks on animal and comparative physiology are considered classics, remarkable in their readability and enthusiasm. "I envy his ability to make this arcane stuff intelligible," says anatomist William Jungers of the State University of New York at Stony Brook. Two decades ago, for instance, Schmidt-Nielsen wrote a short book ambitiously titled *How Animals Work*. The book became an instant hit. The Japanese scientists and officials on the prize committee evidently agreed that there could have been no better author.

–John Travis