NOBEL PRIZES

Nobels Run the Gamut From Cells to the Cosmos

Awards honor new ways of viewing growth and death, particles and waves, the molecules of life, and the roots of economic decisions

Tiny Worm Takes a Star Turn

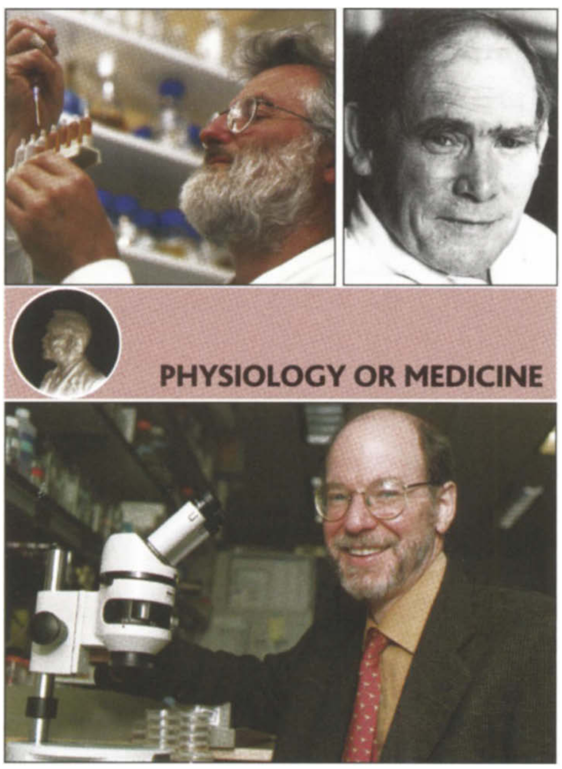
The nematode worm known as *Caenorhabditis elegans* is not much to look at. Just a millimeter long and transparent to boot, it is almost invisible to the naked eye. But in biological research the tiny worm looms large, providing a model system for studying everything from embryonic development to aging. Now, three researchers who pioneered the use of *C. elegans* as a model organism have won the Nobel Prize in Physiology or Medicine.

The Nobel Academy cited the three—Sydney Brenner of the Salk Institute for Biological Studies in La Jolla, California, and the Molecular Sciences Institute in Berkeley, California; H. Robert Horvitz of the Massachusetts Institute of Technology (MIT) in Cambridge; and John Sulston of the Wellcome Trust Sanger Institute in Cambridge, U.K.—particularly for discoveries concerning the genetic regulation of organ development and programmed cell death, a type of cellular suicide that helps sculpt the organs of developing organisms and regulate cell growth in mature ones.

"I was just jumping for joy all day," says Judith Kimble of the University of Wisconsin, Madison, who has studied *C. elegans* for more than 2 decades. Long-time cell death researcher Stanley Korsmeyer of Harvard's Dana-Farber Cancer Institute is also thrilled. "It's a wonderful thing for both [the cell death and worm] fields," he says.

Brenner won special plaudits for recognizing the potential of *C. elegans* in biology and then developing it as a model in work that dates back to the 1960s, when Brenner was at the MRC Laboratory of Molecular Biology in Cambridge, U.K. Early on, Horvitz recalls, many researchers viewed the worm as "Sydney's idiosyncrasy," lagging too far behind the fruit fly to contribute much to genetic studies. But that didn't faze Brenner. "In the case of Sydney Brenner, this award has been so overdue," notes worm researcher Martin Chalfie of Columbia University in New York City.

C. elegans makes a good experimental model precisely because it is so small—it contains only about 1000 cells—and because its life-cycle lasts just 3.5 days. Yet the worm is complex, consisting of a variety of cells and tissues, including a nervous system. These qualities make it easy for researchers to trace the cellular effects of mutations, thus opening the way to identifying the genes involved in development of the different cell types. Brenner gave the work an early boost by showing that he could induce mutations in the worm with a chemical known as EMS. The result was what Chalfie calls "a veritable gold mine of genes," many of which turned out to be involved in nerve cell development and function.



Apostles of *elegans*. John Sulston, Sydney Brenner, and H. Robert Horvitz (*clockwise*).

Sulston joined Brenner's Cambridge group in 1969. Over several years, he traced the lineages of the cells that form the worm's nervous system and then completed tracing the lineages of all the cells that make up the adult worm. Although difficult and painstaking, Sulston says, the work was far from tedious. "For me, it was absolutely entrancing," he recalls. "Because one feels it is all going forward, it is worth doing."

Among other important findings, the lineage work showed that each individual worm is formed by exactly the same series of cell divisions. In addition, Sulston found that 131 cells, mostly those in the nervous system, undergo programmed cell death. Neurobiologists already knew that neuronal death helps form the nervous systems of mammals, but now researchers had an animal with which to explore the hows and whys of that cell death.

That's where Horvitz's contribution comes in. After completing his graduate work at Harvard in 1974, Horvitz joined Brenner's group in hopes of using *C. elegans* to study the nervous system. While in Cambridge he helped with Sulston's lineage-mapping project, and on taking a faculty position at MIT in 1978 began a series of studies aimed at identifying developmental mutations in the worm. By the mid-1980s, that work led him to two genes, *ced-3* and *ced-4*, needed for normal cell death during *C. elegans* development, plus a third, called *ced-9*, that protects against cell death.

Horvitz "was the first to show that there was a genetic basis for cell death," says Vishva Dixit of Genentech Inc. in South San Francisco. "The discovery really illuminated a new pathway to explore." Researchers soon found that mammalian cells contain similar death genes.

Disturbances in cell death pathways have medical implications. Excessive death has been linked to the neurological damage of stroke and Alzheimer's disease, for example, and cancer may result if cells fail to die when they should. Researchers are now exploring ways to treat neurological diseases by blocking cell death and, conversely, to trigger it in cancerous tumors. "In a relatively short time we came from a genetic basis [for cell death] to therapeutic consequences," Dixit says.

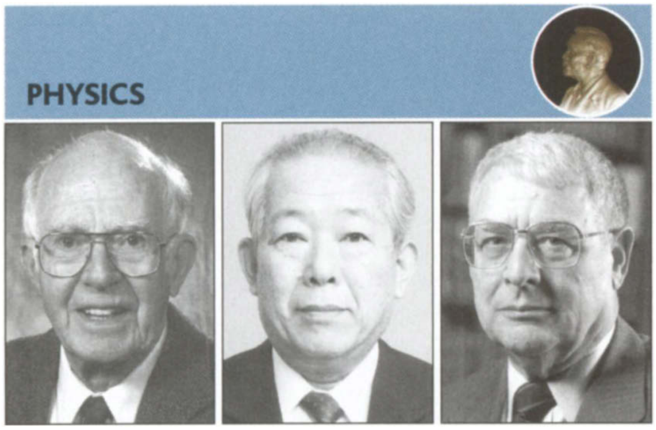
Although the Nobel Committee focused on cell death, Chalfie and others point out that the three new laureates have made other major contributions. For example, Sulston was a prime mover behind the recently completed sequencing of the human and worm genomes—work not mentioned in the Nobel citation—and Horvitz helped trace out an important pathway that regulates development both in the worm and in higher organisms. Says cell death researcher Dale Bredesen of the Buck Institute in Novato, California: "There's no question that these guys have done very exciting work that spans cell death and many other areas as well."

–JEAN MARX

CREDITS: (SULSTON) THE WELLCOME TRUST MEDICAL PHOTOGRAPHIC LIBRARY; (HORVITZ) DONNA COVENEY/MIT/AP

Neutrino Traps and X-ray Eyes

Three physicists have won the ultimate scientific accolade for giving humanity new eyes. Half of this year's Nobel Prize in Physics went to Ray Davis of the University of Pennsylvania, Philadelphia, and Masatoshi Koshiba of the University of Tokyo for using neutrinos to gain insight into the cosmos. The other half went to Riccardo Giacconi of Associated Universities Inc. (AUI) of Washington, D.C., for a 4-decade-long effort to view the universe with x-ray spectacles.



Cosmic vision. Ray Davis, Masatoshi Koshiba, and Riccardo Giacconi (*left to right*).

Davis and Koshiba dedicated their careers to hunting neutrinos, nearly massless elementary particles. When Davis started his quest in the late 1950s, physicists knew that Earth must be flooded with neutrinos emanating from the sun, but nobody knew how to detect them. Davis realized that he could use a rare reaction in which a neutrino strikes a chlorine atom, turning a neutron into a proton to produce argon, to sense neutrinos created by the decay of boron-8 in the sun.

Deep in the Homestake Gold Mine in South Dakota, Davis filled a 37,850-liter tank with chlorine-rich fluid and then painstakingly scoured it for mere handfuls of argon atoms. After decades of effort, Davis showed, to physicists' shock, that Earth was being pelted with roughly a third as many neutrinos as theory predicted. This "solar neutrino problem" became an enduring puzzle in physics—and one of the first signs that neutrinos have mass.

Koshiba and colleagues took the next step. They, too, used a mine to shield a vast tub of fluid from cosmic rays and radiation. But instead of chlorine, the Kamiokande detector, built near Kamioka, Japan, in 1982 and 1983, sought traces of neutrinos in water.

When a neutrino hits a particle in a tank of water, the collision can trigger a brief flash—the optical equivalent of a sonic boom. By detecting flashes with sensitive photodetectors, the Kamiokande team could not only detect neutrinos, but also tell where they were coming from. Kamiokande confirmed Davis's solar-neutrino paradox and later spotted neutrinos from Supernova 1987A, an exploding star 170,000 light-years away. Successors to Davis's and Koshiba's experiments are revealing the nature of neutrinos and shedding light on processes deep inside the sun. Among other things, they have solved the solar-neutrino paradox by showing that neutrinos change type, or "flavor," en route from the sun to Earth. Davis and Koshiba "have an important part in the history of the subject," says physicist John Bahcall of Princeton University. "[Their work] won't be described by paragraphs in the textbooks, but by chapters."

While Davis and Koshiba were equipping astronomers with neutrino eyes, Riccardo Giacconi worked with light—but light of a particularly troublesome type. Unlike visible light, x-rays are absorbed by the atmosphere and zoom right through mirrors. Their bothersome optical properties made x-ray astronomy impractical until scientists could loft compact detectors above the atmosphere. In 1962, Giacconi loaded a sensitive version of a Geiger counter aboard a sounding rocket. After two failed launches, the Aerobee rocket soared to 224 kilometers above Earth and, for the first time, saw x-rays emanating from the sun.

In 1960, Giacconi and Bruno Rossi of the Massachusetts Institute of Technology (MIT) figured out a clever way to focus x-rays onto a detector by skimming them along a surface, rather than bouncing them off a mirror as in conventional optics. The technique dramatically increased the sensitivity of x-ray telescopes. Since then, Giacconi has been involved in most of the major advances in x-ray astronomy, including 3 decades of satellite observations that have given astronomers crucial information about black holes, star formation, galactic nuclei, and other energetic events and objects. "He's an excellent choice. It's one of those cases that many of us thought should have happened years ago and then we gave up hope," says Claude Canizares, an x-ray astronomer at MIT. "He's just a giant in the field."

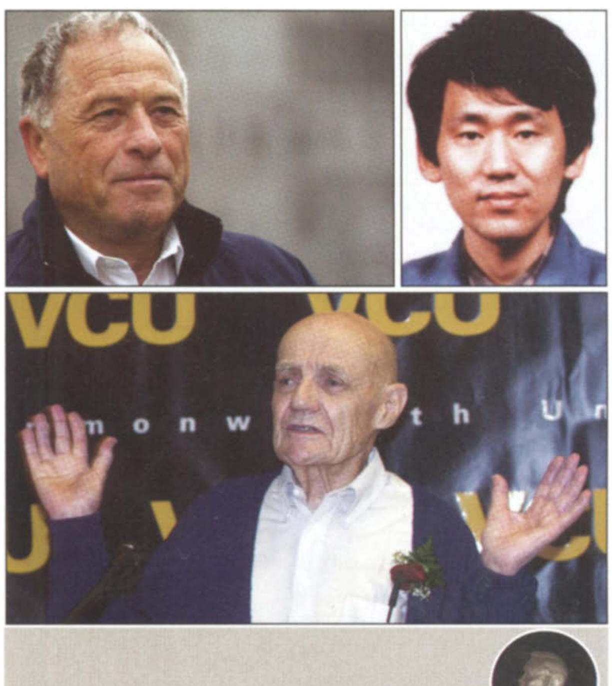
Giacconi—who went on to run NASA's Space Telescope Science Institute in Baltimore, the European Southern Observatory in Munich, and now AUI, the organization that manages the National Radio Astronomy Observatory—is just pleased to have been a part of such eye-opening research. "X-rays give you the key to phenomena of cosmic evolution," he says. "I was lucky enough to get involved right at the beginning."

—**CHARLES SEIFE**

Mastering Macro-Molecules

With the genomes of several organisms in the bag and others soon to follow, biologists are turning their attention to the myriad proteins those genes create. Researchers in the burgeoning field of proteomics are working to determine the sequence of amino acids that make up each giant protein molecule and to deduce the molecule's shape, which determines how it behaves. This year's Nobel Prize in Chemistry honored three researchers whose discoveries have made such studies possible.

Half of the prize went to John Fenn of Virginia Commonwealth University in Richmond and Koichi Tanaka of Shimadzu Corp. in Kyoto, Japan, who independently developed techniques to ionize large molecules such as proteins. Kurt Wüthrich of the Swiss Federal Institute of Technology in Zürich re-



Proteomics pioneers. Kurt Wüthrich, Koichi Tanaka, and John Fenn (*clockwise*).

CREDITS: (DAVIS) UNIVERSITY OF PENNSYLVANIA; (GIACCONI) ASSOCIATED UNIVERSITIES INC.; (WÜTHRICH) MICHELE LIMINA/KEYSTONE/AP; (TANAKA) SHIMADZU CORP; (FENN) STEVE HELBER/AP ceived the other half for developing nuclear magnetic resonance (NMR) techniques that reveal the molecules' shapes.

Working independently, Fenn and Tanaka discovered ways to give huge molecules an electrical charge without ripping them apart. The charged molecules, or ions, can then be fed into a mass spectrometer to determine their masses and, after further analysis, their amino acid sequences. Such studies wouldn't work without the prize-winning innovations, says John Yates, a mass spectrometrist at the Scripps Research Institute in La Jolla, California. "The ionization techniques are the horses that pull the cart," Yates says.

Fenn's technique, called electrospray ionization, begins with a solution of the molecules. A high voltage draws electrically charged droplets from a hollow needle, and these quickly evaporate, leaving behind the freely floating ions. Tanaka's technique, soft laser desorption, begins with a mixture of the jumbo molecules and smaller, light-absorbing molecules on a surface. A blast of laser light heats the absorbing molecules, causing tiny explosions that charge the big molecules and loft them into the air. Since their invention in 1987, the two techniques have become ubiquitous in academic and pharmaceutical laboratories.

In the 1980s Wüthrich found ways to determine the shape of a very large biomolecule by studying how the hydrogen nuclei within it wobble when exposed to carefully tuned magnetic fields, a phenomenon known as NMR. Because the rate of nuclear wobble depends on the strength of both the applied fields and the magnetic fields from nearby atoms, each hydrogen nucleus will move at a slightly different rate and give off a radio signal of a slightly different frequency. Wüthrich found that he could match the different signals with individual nuclei and that correlations between signals could reveal the location of each hydrogen nucleus—and thus the structure of the molecule. "He really has started a new field, and the field is pretty big," says Ad Bax, a biophysicist at the National Institute of Diabetes and Digestive and Kidney Diseases in Bethesda, Maryland.

All three laureates say the award took them by surprise. During a hastily called press conference at Shimadzu headquarters, Tanaka appeared unshaven in the gray corporate uniform common among ordinary company employees in Japan. "If I had had any idea," he said, "I would have put on a proper suit." Wüthrich, 64, says his secretary "broke all the well-established rules" and called him out of a student seminar to relay the phone message from the Royal Swedish Academy. "I think I have not fully realized that I got it," he says.

Tanaka, 43, did his award-winning work in his late twenties. In contrast, Fenn was nearly 70 when he developed his technique. The 85-year-old says he has derived great satisfaction from the utility of his idea, but he's equally happy to get the prize. "The fame is nice," Fenn says, "and I'll enjoy it."

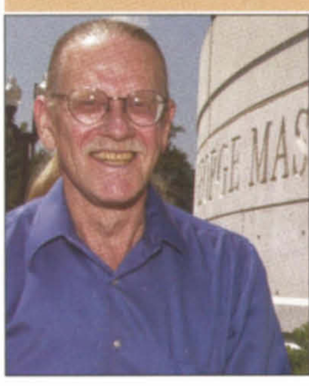
—ADRIAN CHO AND DENNIS NORMILE

Lab-based Researchers Earn Prize in Economics

The Nobel Prize in Economics this year goes to pioneers in two fields that many economists believe are more than ripe for recognition. The $1.1 million bounty will be shared by Daniel Kahneman of Princeton University in New Jersey, who has integrated psychology into economic theory, and Vernon Smith of George Mason University in Fairfax, Virginia, who has turned economics into an experimental science.

Kahneman's selection "was no surprise," says Princeton economist Michael Rothschild, who says he and a number of others had bet on him in the economics department's Nobel pool. People have been impressed by his work for the past 30 years, says Rothschild, but "it took a long time" for researchers to figure out how to integrate it into economics. The honor for Smith (who says, "I've been hearing this rumor since 1980") is also "long overdue," says economist Charles Plott of the California Institute of Technology in Pasadena.

ECONOMICS



Big gains. Daniel Kahneman (*top*) and Vernon Smith (*left*) expanded what economists study.

Economic theory supposes that individuals act with perfect rationality in seeking to optimize their gains. But cognitive psychologist Kahneman, 68, working with Amos Tversky of Stanford University, who died in 1996, identified various nonrational "heuristics"—or mental shortcuts—people use in arriving at decisions, especially in uncertain situations.

Kahneman has demonstrated, for example, that people are generally more adverse to the risk of losing something than they are attracted to the idea of gaining the same thing. Students who had been given coffee mugs at the beginning of an experiment wanted twice as much money to part with them as mugless students were willing to pay to acquire one.

Kahneman also showed that people's willingness to accept risk depends on how different options are phrased. Presented with an epidemic that threatens to kill 600 people, subjects must choose between one response that saves two-thirds of the population and another that may save all but could save just one-third. People choose definite numbers if the options are expressed in numbers of lives saved, but gamble when the outcome is presented in terms of deaths. Kahneman's work, says the Bank of Sweden committee that bestows this prize, has given rise to a whole new field of "behavioral economics."

The work complements research by Smith, 75, who has demonstrated that—contrary to many economists' assumptions—economic behavior could be dissected in the lab. "Smith initiated the notion that you could actually use experiments to check the predictions of economic theory, particularly the actions of markets," says Rothschild.

Smith's experiments, which he refers to as "wind tunnels" of economics, have ranged from testing competing models for energy deregulation to allocation of airport gate time slots. The Nobel Committee says that Smith's work has opened up vast new possibilities in the auction world. He has shown experimentally, for example, that "two-sided" auctions such as the stock market (in which both bidders and askers are yelling out prices) function even with small numbers of players. Smith says his findings have led to the design of new auction systems covering goods from utilities to electromagnetic spectra.

Rothschild says the field of economics is moving more to the experimental and the behavioral. Indeed, the next prize may not even be in economics, says Smith: "There is interest in the [prize committee] in moving the economics prize to a more general social science award."

—CONSTANCE HOLDEN

CREDITS: (KAHNEMAN) DANIEL HULSHIZER/AP; (SMITH) GEORGE MASON UNIVERSITY