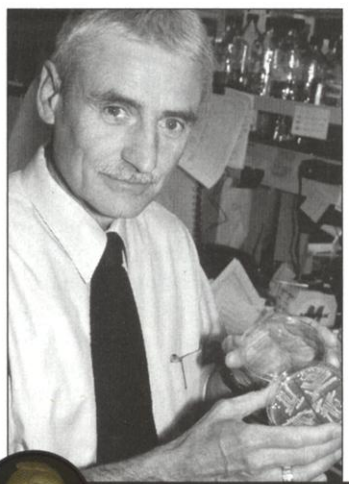
NOBEL PRIZES

Science Awards Pack a Full House of Winners

Three new laureates per prize—the maximum number Nobel rules allow—gain recognition for fundamental advances in their fields

Cycling Toward Stockholm

LONDON—Paul Nurse and Tim Hunt have been good friends for nearly 20 years. Indeed, they have much in common. Both have conducted pioneering research into the intricate molecular choreography that drives cell division. Both work for Britain's Imperial Cancer Research Fund (ICRF): Nurse as its director-general and Hunt as head of ICRF's Cell Cycle Control laboratory in South Mimms, north of London. "We are very complementary," Nurse tells a visitor who has come to see the pair in Nurse's London office, overlooking the lush green gardens of Lincoln's Inn Fields. Now, Nurse and Hunt have something else to share. With yeast geneticist Leland Hartwell, director of the Fred Hutchinson Cancer Research Center in Seattle, Washington, they have been awarded this year's Nobel Prize in physiology or medicine for identifying the key molecular steps in the cell cycle.



MEDICINE

Cell mates. Leland Hartwell (*left*); Paul Nurse and Tim Hunt (*bottom*, left to right).

The winners' work led to the revelation that the cell cycle is controlled through the cooperation of two sets of proteins: the cyclins and enzymes called kinases. Their discoveries not only illuminated cell biology's most fundamental process—the ability to grow and divide—but also have had important implications for medicine. "The principal problem in cancer cells is they divide when they shouldn't," says cell biologist Ted Weinert of the University of Arizona in Tucson. "Without these discoveries, cancer research would still be in the dark ages."

Things were dark indeed in the late 1960s, when Hartwell began his work in yeast genetics. "People knew there was a cell cycle, but as for how to get at the genes, it didn't cross anyone's mind that it was even possible at that point," Weinert says. Hartwell's research sprang from a project he had assigned to Brian Reid, an undergraduate student in his new lab at the University of Washington, Seattle. "I gave him mutant [yeast strains] that formed very odd shapes at high temperatures," Hartwell recalls.

The oddly shaped cells, it turned out, were having trouble dividing. After one or two generations, for example, each would have a very large bud, which had failed to separate and become a daughter cell. "We were immediately stunned by the amount of information they gave us on cell division," Hartwell says. They could see the physical consequences of the mutation as well as at what point in the cell cycle the mutation exerted its effect. By the early 1970s, the Hartwell lab had identified dozens of gene mutations that disrupt the cell cycle, although the nature of the proteins encoded by these "cell division cycle" (*cdc*) genes wasn't known.

While Hartwell was making his seminal discoveries, Nurse was completing his graduate studies in amino acid metabolism at the University of East Anglia in Norwich, U.K. But the lab's amino acid analyzer kept breaking down, and Nurse had to spend many hours babysitting the machine. This gave him plenty of time to read journal articles, including Hartwell's early papers. "I saw that this genetic approach is really powerful," Nurse says.

After receiving his Ph.D., Nurse began working at the University of Edinburgh, U.K., searching for cell cycle genes in the fission yeast *Schizosaccharomyces pombe*. Like Hartwell, he soon identified a number of *cdc* genes, as well as so-called "wee" mutations that caused the yeast to go into mitosis early, stunting the growth of the cells. When one of these mutated genes, *wee2*, turned out to be a mutant form of a gene Nurse had isolated earlier called *cdc2*, he reasoned that *cdc2* must control when mitosis begins.

Subsequent work revealed that *cdc2* operates as a master control switch that determines the timing of key steps in cell division. Moving on to the University of Sussex, and later to Oxford and London, Nurse and his co-workers found that the *cdc2* gene codes for a protein called a kinase, part of a family of regulatory enzymes important to many cell functions. The group also showed that *cdc2* is nearly identical to Hartwell's *cdc28* gene in bakers' yeast.

In the meantime, Hunt, who had received his Ph.D. from Cambridge University, began spending summers at the Marine Biological Laboratory in Woods Hole, Massachusetts. He was trying to figure out how fertilization of the sea urchin egg triggers protein synthesis, one of the first steps in the development of the sea urchin embryo. But the work seemed to be going nowhere. Then, in 1982, Hunt tried what he now calls "a completely off-the-wall" experiment "of the desperate variety."

He decided to compare the protein synthesis patterns in fertilized eggs with those that developed parthenogenetically—that is, without fertilization. The results, he says, were a "complete revelation." In the fertilized eggs, the levels of a protein present in high concentrations dropped drastically just when the cells divided. Then the levels rose again, only to drop at the next round of cell division. Hunt named this protein cyclin, the first of many such proteins to be discovered.

It soon emerged that Hunt and Nurse were independently looking at two facets of the same problem. Further work showed that cyclins regulate the enzymatic activity of the Cdc2 protein and other so-called cyclin dependent kinases (CDKs). In fact, Cdc2 and its cyclin regulators actually join together to form a larger molecular complex called maturation promoting factor (MPF). MPF—which had first been identified as the key initiator of cell division in frog eggs in the early 1970s by the Japanese scientist Yoshio Masui—had long resisted biochemical analysis. Now, that mystery was solved.

In 1987, when Nurse isolated the human

CREDITS: (TOP TO BOTTOM) FRED HUTCHINSON CANCER RESEARCH CENTER; AP PHOTO/ALASTAIR GRANT

version of Cdc2—called CDK1—it also became clear that the cell cycle is controlled by a universal mechanism that has been conserved in yeast, amphibians, mammals, and other organisms over nearly 2 billion years of evolution.

Since then CDKs, cyclins, and their associates have been at the center of research on both normal and cancerous cell growth. "If you said, 'Let's give a prize for CDK,' these are the three people you would give it to," says cell biologist Kim Nasmyth of the Research Institute of Molecular Pathology in Vienna, Austria. "I think [the Nobel committee] got it absolutely right." In fact, says cell biologist Joan Ruderman of Harvard University, who worked with Hunt on some of his early studies, the whole field is enjoying the moment in the spotlight. "For many of us, it feels like cyclin/Cdc2 has won the Nobel Prize, and we are all very happy about that!"

–MICHAEL BALTER AND GRETCHEN VOGEL

Laurels for a New Type of Matter

Wolfgang Ketterle, Eric Cornell, and Carl Wieman have gotten a warm reception for their chilly work: They have won the 2001 Nobel Prize in physics for creating the first Bose-Einstein condensates (BECs) in gases of rubidium, sodium, and other alkali metals.

"It's very well deserved," says Claude Cohen-Tannoudji, a physicist at the École Normale Supérieure in Paris. "There [are] a lot of new directions being explored" because of BECs, he adds.

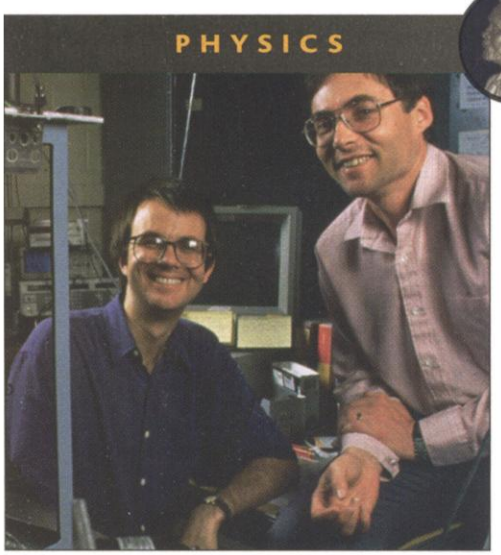
By cooling gases to a few billionths of a degree above absolute zero and coaxing them into forming a new state of matter, the three laureates verified a prediction made by Albert Einstein 70 years earlier. Einstein, in turn, took his cue from physicist S. N. Bose, who, in the mid-1920s, investigated the properties of particles that have integer spin—now termed "bosons." Bosons, which include certain atoms, behave differently from their opposite numbers, fermions, which have half-integer spins. Fermions tend to avoid one another; that is why you can fit only a certain number of electrons, which are fermions, into each atomic shell. Bosons, on the other hand, have no such restrictions, so many of them can occupy the same atomic state at the same time.

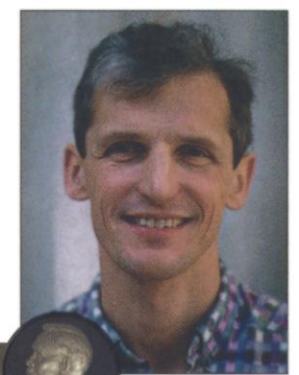
Einstein claimed that when cooled enough, bosons in a gas would stop jittering about and settle down into the lowest energy state, or ground state. Thanks to their sociable nature, thousands of bosons could all be in the ground state, forming, in a sense, one large "superboson": a BEC. BECs are playgrounds for bizarre physics. You can manipulate a BEC to create a very fine interference pattern, slow light down to a crawl within it (*Science*, 27 July, p. 663), or use it as an almost macroscopic testing ground for quantum mechanics. "We brought it to an almost human scale," says Wieman. "We can poke it and prod it and look at this stuff in a way no one has been able to before."

For decades, researchers tried to inveigle matter into becoming a BEC, without success. Then, in 1995, Cornell and Wieman, physicists at the University of Colorado, Boulder, used a combination of optical and magnetic trapping techniques to bully about 2000 cooled rubidium atoms into forming a BEC. Shortly thereafter, Wolfgang Ketterle of the Massachusetts Institute of Technology created a considerably bigger BEC cloud out of sodium atoms. Those achievements set off a flurry of experiments in which teams watched BECs interfere with themselves, used them to create "atomic lasers," and watched as vortices formed and dissipated within the BECs. Researchers have also added new atoms to the roster of BEC-producing gases, including isotopes of hydrogen, lithium, and most recently potassium (www.sciencexpress.org). "We've been surprised to see the explosive growth of the field," Ketterle says. "We thought it would be neat, but it has had an enormous impact on atomic physics."

The prize, split evenly among the three winners, comes as no surprise to the physics community. In 1997, Cohen-Tannoudji, along with physicists Steven Chu of Stanford University and William Phillips of the National Institute of Standards and Technology in Gaithersburg, Maryland, won the Nobel Prize in physics for developing the cooling techniques that enabled physicists to make BECs. That prize was widely seen as an early acknowledgment of the importance of BEC research. Now the other shoe has dropped, and the physicists who created the first BECs can bask in glory that is far more than cold comfort.

–CHARLES SEIFE





Matter masters. Wolfgang Ketterle (*above*); Eric Cornell and Carl Wieman (*below*, left to right).

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A special Web feature on this year's physics laureates, including research, news, and commentary from the pages of *Science*, can be found at www.sciencemag.org/feature/data/nobelprize/2001/physics.shtml.

Chemists Hear One Hand Clapping

Pioneers of chemical handedness received their own round of applause from Stockholm last week. A pair of U.S. researchers William Knowles, now retired from Monsanto in St. Louis, Missouri, and K. Barry Sharpless of the Scripps Research Institute in La Jolla, California along with Japanese chemist Ryoji Noyori of Nagoya University won this year's Nobel Prize in chemistry for creating catalysts that can produce a particular geometric form of a compound without creating its mirror-image partner. The work has proved vital for the production of everything from pharmaceuticals and flavorings to advanced materials and insecticides.

George Whitesides, an organic chemist at Harvard University, says the Nobel committee likely had a difficult choice because other researchers, including French chemist Henri Kagan, also played important roles in developing such catalysts. Kagan, Noyori, and Sharpless received this year's Wolf Prize in chemistry, often seen as a predecessor to the Nobel. Nevertheless, Whitesides says he is "delighted" that Sharpless, Noyori, and Knowles were honored. "This combination of guys put together what has become a dominant theme in organic synthesis. It has motivated the chemical community for a number of years."

Chemists have known since the 1870s that molecules can come in more than one mirror-image form. This property, known as chirality, is widespread in biology: DNA, proteins, and sugars all boast mirror twins. In some cases this slight structural difference can lead to dramatic consequences. When the drug thalidomide was given to pregnant women in the 1960s to prevent nausea, one of its mirror-image forms caused birth defects in thousands of children.

At the time, most techniques for making handed molecules produced only mixtures

Handymen. William Knowles, Ryoji Noyori, and Barry Sharpless (*left to right*).

CHEMISTRY

of chiral forms. Attempts to purify out the desired compound were inefficient, costly, and wasteful, says Harvard organic chemist Stuart Schreiber. Knowles set out to make a catalyst specific to one side of the mirror. He worked on one that added hydrogen atoms to molecules harboring pairs of carbon atoms. The carbon pairs sit in a flat plane, and the hydrogens poke out either above or below—which way determines the handedness of the final compound. Other early catalysts attached hydrogens to either side indiscriminately. But in 1968 Knowles came up with a novel version which, he says, "was shaped so that it could only come in on one side." He soon used this strategy to devise an industrial process to make L-dopa, an amino acid useful in treating Parkinson's disease.

Noyori later expanded on Knowles's early work to create more broadly useful hydrogen-adding chiral catalysts that are still widely used in industry today. For their work, the Royal Swedish Academy of Sciences awarded them half of this year's chemistry prize. Sharpless earned the other half for creating chiral catalysts that add oxygen to precursor molecules. That has proven to be an even more versatile tool, says Whitesides, because it creates chiral building blocks that can be easily modified further to make a wide range of materials and drugs. "Chemists used those to solve a bunch of synthetic problems that had previously been insoluble," he says.

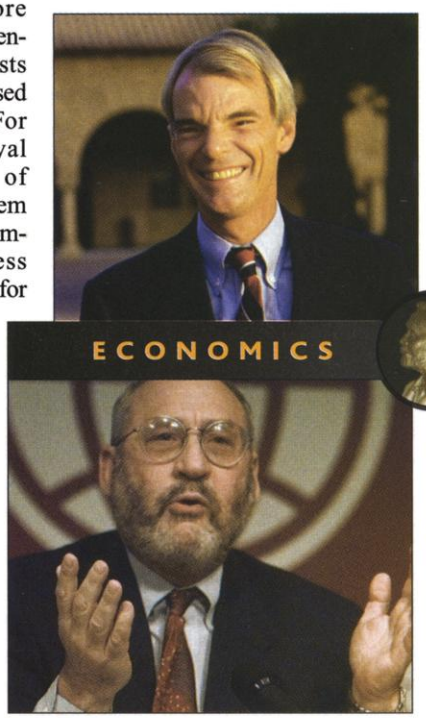
–ROBERT F. SERVICE

ECONOMICS

Knowledge Is Power

In classic economic theory, there are no secrets; everybody knows what everybody else knows. The real world, of course, doesn't work that way. In most market settings, one side knows more than the other: a car dealer, say, who knows he's unloading a lemon, or a job applicant who knows how hard a worker she really is. Economists began exploring the implications of "asymmetric information" in the 1970s. The fruits of their labors have now netted three of them a Nobel Prize.

The latest laureates are George Akerlof of the University of California, Berkeley, Michael Spence of Stanford University, and Joseph Stiglitz of Columbia University. Their findings undercut many once-cherished assumptions of economics, explains Andrew Weiss of Boston University, including the mantric "law" that supply equals demand, which may not hold when information is unequally held. "This is absolutely revolutionary work," Weiss says. "It changes the way we teach economics."



Balancing act. Michael Spence, Joseph Stiglitz, and George Akerlof (*counterclockwise*).

Akerlof's groundbreaking work, a 1970 essay titled "The Market for Lemons," which the Nobel Prize committee calls "the single most important study in the literature on economics of information," showed how asymmetric information can create a market in which supply and demand are out of whack. If buyers can't tell the difference between a peach and a lemon (until it's too late), they won't be willing to pay what a peach is actually worth. As a result, the sellers of peaches retreat from the market, leaving only lemons—even though demand for peaches is still strong. A recent, costly example involves the information technology (IT) sector of the economy itself: When prominent but unprofitable IT "lemons" began going belly up, investors realized they had no way of distinguishing them (in advance) from profitable ventures and pulled out altogether.

One way to cope with asymmetric information is for informed parties to "signal" their information. In his 1972 dissertation, Spence analyzed how job applicants use educational attainment to signal their potential productivity. Racking up an advanced degree or a grade-inflated GPA may not mean you know anything useful, but it presumably says something about your work ethic. Spence found that informed parties can be driven to overinvest in such signals—be it a person who gets more education than he or she needs or a company that posts a big dividend instead of expanding, just to show investors it's making a profit. "Mike's fundamental insight lets us understand a huge range of real world phenomena," says Stanford colleague John Roberts. "Such insights come very, very rarely."

Uninformed parties can also elicit information from the other side. In a 1976 paper co-authored with Michael Rothschild of Princeton University, Stiglitz showed how insurance companies do this. By offering, for example, high-premium/low-deductible vs. low-premium/ high-deductible car insurance, companies in effect get customers to declare how risky or safe a driver they are.

Revolutionary as it was, asymmetric information is now widely accepted. "It's part of the canon of economic theory," Rothschild says. What remains to be seen is whether the supply of new ideas can meet the demand for solutions to economics problems.

–BARRY CIPRA

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