Nine Make the Nobel Grade

This year, Nobel Prizes in science and economics went to pioneers in developmental biology, atmospheric chemistry, and rational behavior, and to the discoverers of two elementary particles

FLY DEVELOPMENT WORK BEARS PRIZE-WINNING FRUIT

Does the family of genes that determine where an insect sprouts wings also tell fish where to grow fins? Are the molecules that map out the body plan in an embryo later required to produce specific organs and tissues and to help cells communicate with each other? Today questions such as these preoccupy developmental biologists around the world, yet few researchers would be asking—and answering—them had it not been for pioneering studies done between the 1940s and the 1970s showing how a few genes control the embryonic development of fruit flies.

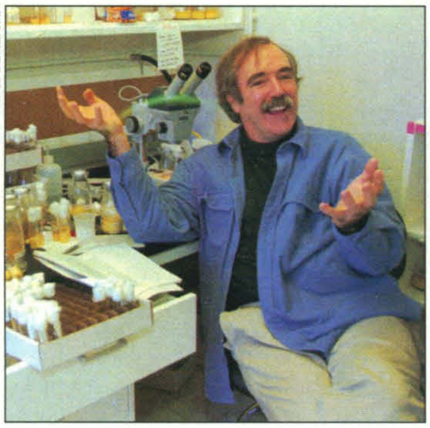
Now the Nobel Assembly in Stockholm has honored the scientific pioneers responsible for these studies. This year's Nobel Prize in physiology or medicine went to developmental geneticists Edward B. Lewis of the California Institute of Technology (Caltech), Christiane Nüsslein-Volhard of the Max Planck Institute for Developmental Biology in Tübingen, Germany, and Eric Wieschaus of Princeton University, all of whom identified genes that affect development in the fruit fly *Drosophila melanogaster*.

The selection is the first honoring basic developmental research since 1935. The field "hasn't been recognized very much" by the Nobel Assembly, says Nüsslein-Volhard, but now the award will help her spread the message that "basic research ... is really worth doing. And if you have a Nobel Prize I guess people listen a bit more carefully to what you say." More than just a capstone to a career in science, adds Lewis, who at age 77 is a professor emeritus at Caltech, the award is "a recognition of the power of pure genetics."

And other researchers think it would be hard to imagine better recipients. Their work "has had a huge impact on the field," says Richard Losick, a developmental biologist at Harvard University. "It's made it possible to understand how you get from a fertilized egg to a multicellular creature with specialized types of cells." Adds developmental geneticist Wolfgang Driever of Massachusetts General Hospital in Boston, "If you went through a modern textbook in developmental genetics and took out all the pages that couldn't have been written if these three people hadn't been around, there wouldn't be much left."

Subsequent work by the Nobelists and others has shown that genes similar to the ones that determine body pattern in *Drosophila* are at work in vertebrates, including mammals, and even in plants. Not only the genes and their protein products but also the sequence of their interactions "seem to be highly conserved," says David Hogness, a developmental biologist at Stanford University. Because of this conservation, work that began in the fruit fly is even helping explain defects that could be responsible for some miscarriages and congenital malformations in humans, a connection noted by the Nobel Assembly in explaining their choice.

KARL MATHIS/AP



MIKE DERER/AP

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The fly prize. *(Clockwise from top)* Edward B. Lewis, Christiane Nüsslein-Volhard, and Eric Wieschaus unraveled the genetics of *Drosophila* development.

The three winners, although of different generations, share a combination of courage and endurance. Lewis chose early in his career to study an odd class of fruit fly mutations in which entire body parts, such as an extra pair of wings, appear in unexpected locations. Called "homeotic" mutations (from the Greek for "likeness"), such changes were ascribed by many molecular biologists to simple coding errors within a single gene-protein system. But Cambridge University geneticist Michael Ashburner says that "Ed had the insight, right from the 1940s, that the homeotic genes were not just a curiosity—that their organization would be deeply interesting in a biological sense."

Lewis realized that in flies with an extra pair of wings an entire segment of the thorax had been omitted and replaced by a duplicate of the segment just in front of it. Over decades, Lewis collected and crossbred flies with other mutations that altered segment identities, classifying the abnormalities and mapping the locations of the affected genes along the fly's third chromosome. In this manner, he identified a series of control genes (later named "homeotic selector genes") that seemed to regulate the activity of other genes, eventually guiding the development of specialized features within each body segment (*Nature*, 7 December 1978, p. 565). Lewis also demonstrated the "colinearity principle": that homeotic selector genes appear on the chromosome in an order corresponding to the order of the body segments they influence (see diagram). This arrangement is possibly maintained because the regulatory regions that turn these genes on and off overlap. (The homeobox, a section of DNA that helps specify cell fate, was first detected in homeotic selector genes.)

But Lewis's work didn't explain crucial events upstream from this selector gene activity: the genetic changes that divide the embryo into primordial segments and lead to selector-gene activation in the first place. That question intrigued Nüsslein-Volhard and Wieschaus, who, in the late 1970s, were young group leaders at the European Molecular Biology Laboratory (EMBL) in Heidelberg, Germany. The two decided to embark on an ambitious "saturation screen" designed to detect all the genes affecting segmentation.

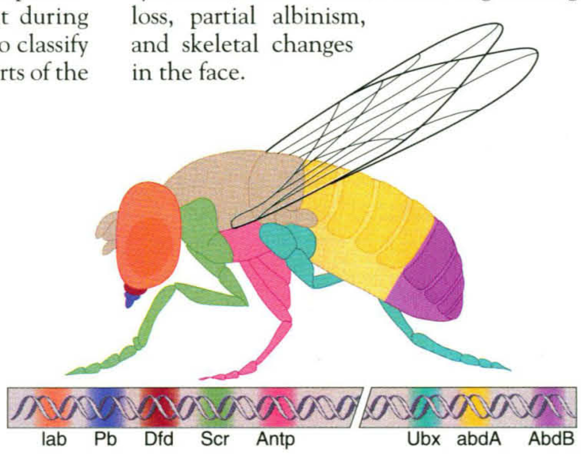
Sitting at a special dual microscope, Nüsslein-Volhard and Wieschaus spent a year scanning thousands of dead *Drosophila* embryos—the second-generation offspring of flies exposed to mutagenic chemicals—for signs of defects in cuticle formation that would indicate abnormal segmentation. Explains Wieschaus, "We would ask, do the embryos of a given stock look abnormal in the same way? Is there a mutant phenotype that did something constant during development? Then we would try to classify the defects." Determining which parts of the embryo were deleted by lethal mutations, they hoped, would indicate how the affected genes normally function.

The project was a risky one, both scientifically and professionally. The screen could have turned up too many segmentation genes to fit into a meaningful classification scheme. And "in the context of a molecular biology lab, it was seen as a little weird" for the two scientists to restrict themselves entirely to genetic techniques, recounts Hermann Steller, a developmental neuroscientist who joined EMBL as a graduate student in 1981 and is now at the Massachusetts Institute of Technology.

But the saturation screen was "a phenomenally well-organized frontal assault on a problem, and relatively shortly into it they already knew they'd hit the jackpot," says Mark Peifer, a developmental biologist at the University of North Carolina, Chapel Hill, and a former postdoc in Wieschaus's lab at Princeton. That jackpot showed up when Nüsslein-Volhard and Wieschaus saw that their mutant flies fit into three distinct categories—which they named "gap," "pair-rule," and "segment polarity"—and proposed that three corresponding sets of genes act at different levels to progressively subdivide the embryo into segments.

According to a model that gained widespread acceptance shortly after the pair's landmark 1980 paper (*Nature*, 30 October 1980, p. 795), differing concentrations of a maternal gene product first activate the gap genes, dividing the embryo into broad regions. Later, the pair-rule genes subdivide these regions into segments, and finally, the segment polarity genes set up repeating anterior-to-posterior structures in each segment. The homeotic genes, identified by Lewis, are turned on in bands defined by the gap genes, and their action is refined by the pair-rule and segment-polarity genes.

"Untold thousands" of researchers are now analyzing the genes and gene families Lewis, Nüsslein-Volhard, and Wieschaus defined in *Drosophila* and their homologs in mice, chickens, zebrafish, humans, and other organisms, Peifer notes (*Science*, 13 May 1994, p. 904). The chicken gene *Sonic hedgehog*, a relative of the fruit fly segment-polarity gene *hedgehog*, for example, has recently been shown to play an important role in determining left-right asymmetry in the early embryo (*Cell*, vol. 82, p. 803, 1995). And mutations in a human gene related to the fruit fly pair-rule gene *paired* can cause Waardenburg's syndrome, a rare disease involving hearing loss, partial albinism, and skeletal changes in the face.



Prize-worthy parallels. Body segments in the fruit fly get their identities from a series of control genes that appear in the same order on the fly's chromosome.

SOURCE: S. GILBERT, *DEVELOPMENTAL BIOLOGY*, SINAVER ASSOC., 1994 ILLUSTRATION: K. SUTLIFF

"This Nobel shows that one door opened by a few original people can do more than a huge number of scientists have done before them," says Peter Lawrence, a *Drosophila* geneticist at the Laboratory of Molecular Biology in Cambridge, England. And once that door is opened, an equally large number of researchers can walk through.

–Wade Roush

CHEMISTRY

Uncovering Threats to the Ozone Layer Brings Rewards

Few scientific discoveries make a splash that ripples far beyond a specialized field, or beyond science in general. But the trio of atmospheric chemists who share this year's Nobel Prize in chemistry were honored for work that triggered scientific and political waves that continue to stir the waters even today. Their research identified chemicals that destroy stratospheric ozone, which shields Earth's plants and animals from harmful ultraviolet radiation. The discovery paved the way for an international agreement to ban the production of ozone-destroying compounds, known as chlorofluorocarbons (CFCs), beginning the first day of 1996.

"[The work] changed the complexion of what controls the global ozone distribution profoundly," says James Anderson, a professor of atmospheric chemistry at Harvard University in Cambridge, Massachusetts. Paul Crutzen, who works at the Max Planck Institute for Chemistry in Mainz, Germany, earned his share of the prize, in part, for his 1970 discovery that a naturally produced compound known as nitrous oxide makes its way to the stratosphere, where it spawns related chemicals that chew up individual ozone molecules. Atmospheric chemists F. Sherwood Rowland of the University of California, Irvine, and Mario Molina of the Massachusetts Institute of Technology won their Nobels for demonstrating in 1974 that industrially produced CFCs also drift up into the stratosphere, where they give rise to ozone-destroying reactions.

By detailing the fragile balance that maintains the ozone layer and showing how activity on Earth was perturbing it, "the three researchers contributed to our salvation from a global environmental problem that could have catastrophic consequences," says a statement from The Royal Swedish Academy of Sciences.

Ozone, a cluster of three oxygen atoms, is concentrated in a layer between 10 and 50 kilometers up. English physicist Sidney Chapman first explained the existence of this layer in 1930 by proposing that the energy from ultraviolet (UV) light converts various forms of oxygen—including atomic oxygen (O), molecular oxygen (O_2), and ozone (O_3)—from one to another, maintaining an equilibrium concentration of ozone. Chapman's mechanism turned out to be correct. But measurements made in the 1950s indicated that ozone concentrations were lower than they should have been. Something other than UV light had to be doing ozone in, researchers concluded, but the culprit remained a mystery.

In 1970, Crutzen pointed to a strong suspect: nitrogen oxides. He was tipped off by research showing that soil bacteria churn out a nonreactive oxide, nitrous oxide (N_2O). In a paper published that year in the *Quarterly Journal of the Royal Meteorological Society*, he outlined a chemical pathway that could transform this ground-produced substance into a high-altitude ozone-eater. He showed that nonreactive N_2O produced by soil bacteria could drift upwards into the stratosphere, where it would be broken apart by sunlight into two reactive nitrogen oxide compounds, NO and NO_2. He then suggested these nitrogen oxides convert ozone molecules into O_2 through a three-step reaction. And because NO and NO_2 are not consumed in the reaction, they continue to break down ozone until they eventually settle out of the atmosphere. By the mid-1970s, atmospheric measurements confirmed Crutzen's conclusions.

It didn't take long for these findings to have a political effect. In 1971, Crutzen's theory was cited by opponents of a U.S. program to build a fleet of supersonic transport (SST) aircraft. The planes were thought to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The high prize. *(From left)* Paul Crutzen identified ozone-destroying reactions in the stratosphere. F. Sherwood Rowland and Mario Molina found some chemicals responsible were humanmade.

pose a grave threat to the ozone layer, as their exhaust would deliver nitrogen oxides right to its heart. (After much debate, the U.S. SST program was abandoned, largely due to fears of noise pollution and high costs.)

The political impact of Crutzen's work foreshadowed the reaction when, in 1974, Molina and Rowland published a paper in the 28 June issue of *Nature* suggesting that humans as well as bacteria were responsible for triggering ozone destruction. Ubiquitous industrial chemicals—chlorine-packed CFCs—traveled a path similar to that taken by the nitrous oxide, and with similar results. "We knew that CFCs would have a long lifetime," as they are chemically very stable, says Rowland. "So we started out to track CFCs from the cradle to the grave. The grave turned out to be the stratosphere." Here, it turned out, CFCs were broken down by UV light, liberating ozone-killing atomic chlorine (Cl) and chlorine monoxide (ClO). "That changed the entire context of global toxicology and showed that what we do on the surface of the Earth could affect the life-support system of the planet," says Anderson.

That stark fact was brought home in 1985, when a team of British researchers discovered the Antarctic ozone hole (see p. 376). CFCs turned out to play a major role in its formation, because they are carried over the pole by global air circulation. Molina went on to help determine that rapid destruction of ozone over the southern pole was largely due to the interaction between tiny ice particles and CFC byproducts such as chlorine nitrate and hydrochloric acid; the interaction transforms them into their more reactive cousins.

Their discoveries also fired up intense political heat to phase out CFCs, a battle that continues to rage today. Last month, for example, the U.S. Congress held hearings on whether the upcoming ban on CFC production should be postponed. Some partisans in this battle even see the Nobel selection as an effort to stave off such a move. "I think the Swedish Academy has chosen to make a political statement," says atmospheric chemist Fred Singer, who has long opposed calls for an early phaseout of CFCs.

But few other researchers see any hint of politics behind the choice of Crutzen, Molina, and Rowland. "I think it's an excellent selection," says Richard Stolarski, an atmospheric scientist at the National Aeronautics and Space Administration's Goddard Space Flight Center in Greenbelt, Maryland. "All three of them did things which formed a turning point in our understanding of the way the atmosphere worked."

–**Robert F. Service**

An Honor for Championing Rational Thought

Erroneous assumptions lead to bad conclusions in any branch of science, but in economics they can lead to disastrous national policies. Many economists believe that's exactly what happened in the 1970s, when governments inflated monetary supplies to create jobs. The bad assumption? That in response to an increased supply of money, consumers would spend more and businesses would take on more workers. Instead, the result was "stagflation"—stagnant economic growth coupled with rapid inflation.


CHARLES BENNETT/AP

Rational reward. For demonstrating that individuals respond sensibly to policy changes, Robert J. Lucas won the economics award.

In the mid-1970s, University of Chicago economist Robert E. Lucas Jr. developed a theory that explained why the assumption was wrong. Individuals, he argued, respond to inflation—an erosion of their buying power—by demanding higher wages, not by spending more; businesses recognize that inflated prices don't indicate increased demand and so do not hire more workers to expand production. These common-sense responses were part of Lucas's theory of "rational expectations," a view of macroeconomics that has garnered Lucas this year's Nobel Memorial Prize in Economic Sciences. In its award citation, the Royal Swedish Academy of Sciences described him as "the economist who has had the greatest influence on macroeconomic research since 1970."

Colleagues agree. "I consider him the economist of his generation, maybe of this half-century," says Edward C. Prescott, professor of economics at the University of Minnesota. "He has had a remarkable influence on economic science," he adds. Lucas's Chicago colleagues are equally fulsome in their praise—"very well-deserved" was the assessment of José Scheinkman, chair of the school's economics department—although praising Nobelists is getting to be routine for Chicago economists. The school's faculty members have won the economics prize in 5 of the last 6 years and eight times since 1976. "I was afraid [the Swedish Academy] might shy away from picking someone at Chicago again so soon," says Lars Hansen, another Chicago economist. "I thought they might make Lucas wait a bit longer." Fortunately for Lucas, that expectation was wrong.

Expectations—erroneous and accurate—are at the heart of Lucas's theory. Until the 1970s, economic policy-makers generally thought they could ignore expectations in their attempts to fine-tune national economies, especially in their embrace of the Phillips curve, an equation implying that jobs could be created through an inflationary monetary policy.

Lucas believed that such an expectation wasn't rational. It "assumed a lot of stupidity on the part of the ordinary citizen," he explained at a press conference in Chicago last week, when the award was announced. His studies demonstrated that workers' rational response—to demand higher wages—would soak up business capital that monetary gurus thought would be used to hire new employees. The result: price inflation without real economic growth. And that was exactly what many economies suffered through the 1970s. "[Lucas] explained the failure," Scheinkman says.

While his analysis of policy-making may be the most visible aspect of Lucas's work, Prescott notes that his influence extends throughout economics. He says Lucas took analytical principles that had been used only in the highly theoretical field of microeconomics and showed how they could be used to solve practical macroeconomic problems. "He has unified economics," Prescott says.

Hansen believes that this blurring of the boundaries of economic subfields is one of the distinguishing characteristics of the atmosphere at Chicago, and something that might be contributing to the school's domination of recent economics Nobels. "Distinctions between fields don't mean much here," he says, adding that everyone is willing to critique the work of colleagues even if it is outside their area of interest. And Lucas doesn't expect any deference on account of his award. "Around here a Nobel Prize doesn't carry much weight in an argument," he said at his press conference. "Around here you've got to win an argument on its merit."

–Dennis Normile

PHYSICS

Particle Hunters Bag Two Trophies—And Share a Third

Martin Perl and Frederick Reines never collaborated. Their experimental techniques were worlds apart, and their achievements, which brought them this year's Nobel Prize in physics, have only two things in common, as far as their colleagues can tell: Both discovered new members of a class of fundamental particles of matter known as leptons (the other basic group is made of quarks), and both prizes are long overdue.

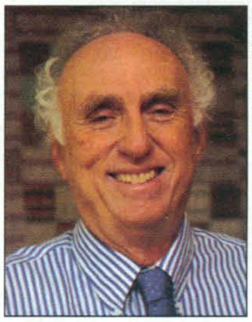
Reines, a professor emeritus of physics at the University of California (UC), Irvine, won his share of the prize for detecting the apparently massless particle called the neutrino. He pulled off this feat in 1956, working with the late Clyde Cowan at the Los Alamos National Laboratory. Perl, of Stanford University and the Stanford Linear Accelerator Center (SLAC), was honored for his role in the discovery of the tau lepton, a close relative of the electron albeit 3500 times heavier. With collaborators at SLAC, Perl pursued his quarry between 1974 and 1977. The discoveries of almost massless and extremely massive leptons set the stage for our current understanding of the relationships among elementary particles, which are divided into three families of two leptons and two quarks each.

As far as the physics community was concerned, those achievements were Nobel-worthy years ago. Columbia University's Mel Schwartz, who shared the 1988 Physics Prize, called it "a fabulous choice," and added "for years, I've been thinking those guys really deserve it." UC Irvine's Henry Sobel, who has studied and worked with Reines on neutrino physics since 1963, said simply, "Better late than never."

Reines's discovery of the neutrino was all the more remarkable because of its elusive nature. Wolfgang Pauli, who first proposed the existence of the particle back in 1930, believed he had done a "frightful" thing by postulating an entity that would likely never be detected. Pauli had invoked the idea to account for the infinitesimal energy and momentum that seemed to be missing in certain radioactive decays of atoms. But the particle has no charge and no apparent mass; it rarely interacts with matter at all, slipping through virtually any detector without a trace.

In 1953, however, Reines and Cowan proposed an ingenious neutrino trap: a 120-gallon tank of water salted with cadmium atoms, surrounded by light detectors. The apparatus would sit next to a nuclear reactor, which theoretically should be emitting hundreds of trillions of neutrinos a second. The goal was to detect flashes of light emitted in the extremely rare instances when a neutrino hit a hydrogen nucleus. Such an interaction, they reasoned, would create two particles, a positron and a neutron. The positron would almost immediately hit an electron, releasing two low-energy photons. But the neutron would take a slower route, plunging through the water until it was captured by a cadmium nucleus; the capture would release high-energy gamma rays. The time delay—a few microseconds—between the photon and the gamma ray releases would be the neutrino's signature. Reines and Cowan were able to identify a few neutrinos each hour. As the Nobel citation put it: "They had raised the neutrino from its status as a figure of the imagination to an existence as a free particle."

UNIVERSITY OF CALIFORNIA, IRVINE



PAUL SAKUMA/AP

Odd couple. Frederick Reines *(top)* found an apparently massless elementary particle of matter, while Martin Perl *(bottom)* found one of the heavier leptons.

Reines went on to pioneer the field of underground physics, building neutrino detectors in the bottom of mine shafts to avoid interference from cosmic radiation, as well as to help kick-start the field of neutrino astronomy. Says Ken Lande, a neutrino physicist at the University of Pennsylvania in Philadelphia: "He has always had novel ideas, novel approaches to doing physics, totally out of the conventional domain."

While Reines worked in small collaborations, Perl did the bulk of his path-breaking physics as a member of the first large American physics collaboration at SLAC. He joined SLAC in 1963, hoping to find heavier versions of the electron, one of which, the muon, was already known. Throughout the sixties, Perl searched through the debris of particle collisions at SLAC for still heavier versions of the electron. But as he puts it, he "couldn't get any leads." Then SLAC started building an electron-positron collider, SPEAR, which operated in a previously inaccessible energy realm, making the detection of a more massive electron possible. Perl and his group hoped to find collisions that produced pairs of muons and electrons together—a combination that could only come from the annihilation of some new heavier lepton in the collision.

Although Perl identified candidate events in the earliest data from SPEAR, he says "nobody believed it at first even at SLAC." It took him months to convince his own collaborators. Finally by late 1974, the group published a paper announcing the discovery, first called the "U" particle for "unknown."

For the next 3 years, says Perl, he had a lot of "sleepless nights" as the physics community seemed more intent on proving him wrong than proving him right. "People kept not finding it," he says. Not until 1977 did Perl finally hear that tau particles had been found at other accelerators and that his discovery had been confirmed.

The discovery of the tau, explains Burton Richter, SLAC's director, "was a complete surprise to physics." By the time it was made, physicists had realized that the existing elementary particle zoo could be divvied up into two families, each with two quarks and two leptons. The lightest family had up and down quarks, and for leptons an electron and an electron neutrino. The heavier family consisted of charm and strange quarks, together with a muon and a muon neutrino. The tau meant there had to be yet a third generation.

As for Perl, he says the Nobel Prize also completes another triad. He got his Ph.D. at Columbia as a student of I. I. Rabi, who won the Nobel Prize in 1944, and his students included Sam C.C. Ting, who shared the prize with Richter in 1976. "So there are three generations, too," says Perl.

–Gary Taubes