NOBEL PRIZES

In Stockholm, a Clean Sweep for North America

This year's Nobel choices strained the prize categories. The chemistry prize recognized techniques that have revolutionized biology and medicine; the physics prize went to a pair of astronomers, and the economics prize honors work on the fringes of history. But one other category held firm: All eight winners did their work in the United States or Canada.

Medicine: Discovery of Genes in Pieces Wins for Two Biologists

There may be many routes to a Nobel Prize, but one of the most direct is to perform an experiment that shatters the strongly held beliefs of an entire scientific discipline. The latest illustration of that principle came this year, with the award of the prize for medicine or physiology to Phillip Sharp of the Massachusetts Institute of Technology (MIT) and Richard Roberts, who recently moved from Long Island's Cold Spring Harbor Laboratory to the biotech firm New England Biolabs in Beverly, Massachusetts. Before 1977, the biology community believed firmly that genes were uninterrupted pieces of DNA that coded for proteins. That year, however, the two molecular biologists, working independently, showed conclusively that a gene is often broken up by lengthy tracts of DNA that do not specify protein structure.


RICK FRIEDMAN


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Splitting the prize. Richard Roberts *(left)* and Phillip Sharp share the Medicine Nobel.

The discovery of these so-called split genes not only dramatically changed how biologists viewed gene structure and function but also had enormous consequences for the study of gene regulation and evolution, and for biotechnology. Indeed, James Darnell of Rockefeller University, whose own data in retrospect hinted that genes contain noncoding sequences, says he doesn't think it's an overstatement to call the work of Sharp and Roberts "the single most surprising and illuminating experiment that has ever been done in biology."

The reason that researchers missed the existence of the protein coding and noncoding regions (later dubbed exons and introns by Harvard University's Walter Gilbert) was that before 1977 molecular biologists had worked mainly on bacteria, and had not gotten a good look at the genes of the more difficult to study higher eukaryotic organisms. Bacterial studies showed that when a gene is activated, its double-stranded DNA is transcribed into a single-stranded mRNA, which is then translated by ribosomes into the corresponding protein. But bacterial genes have no introns.

For their Nobel Prize–winning work, Roberts and Sharp began working with an adenovirus, one of the viruses that cause the common cold. They reasoned that because viruses use the machinery of eukaryotic cells to reproduce themselves, what they learned about viral protein synthesis would also apply to the cells themselves.

To study the relationship between the viral genome and the viral mRNAs, Roberts, Cold Spring Harbor's Thomas Broker, Louise Chow and Richard Gelinas, and Sharp, whose MIT team included Susan Berget and Claire Moore, created hybrid molecules in which an mRNA strand binds to its complementary DNA strand. When they made electron micrographs of these hybrids, the two research groups could see which part of the viral genome had produced the mature mRNA molecule. But the mRNAs didn't line up on the DNAs as expected. Some micrographs, for instance, showed huge loops of unhybridized DNA, clearly revealing that substantial sections of a gene's DNA were ignored in making the final mRNA and thus the protein.

The significance of these pictures was obvious: mRNA synthesis in eukaryotes had to be a great deal more complicated than that in bacteria. "For the first few hours after the discovery was made, Nobel prizes were on everyone's mind," recalls Roberts.

Others were equally impressed. When both groups presented their micrographs at a Cold Spring Harbor meeting in June 1977, biologists realized that their understanding of how genes were structured had been revolutionized. "The audience was just in awe. It was one of those moments where the world is turned upside down," says the University of Colorado's Thomas Cech, who won a 1989 Nobel Prize for his own RNA work.

In the days and months that followed the meeting, other researchers quickly extended the work to the genes of other viruses and of eukaryotic cells themselves. The picture that ultimately grew out of this work, much of it from Sharp's own lab, shows that the mRNAs of eukaryotic cells and their corresponding viruses are synthesized as large mRNA precursor molecules from which the introns are spliced out enzymatically. Only then is the mature mRNA ready to travel to the ribosomes and fashion proteins.

The study of RNA splicing remains a vigorous field to this day. Investigators have learned that varied splicing patterns can allow a single gene to produce multiple proteins with significant differences. Splicing errors have even been shown to result in diseases such as β-thalassemia. Introns are also more than just "junk" DNA, researchers now believe. At the very least, regulatory signals seem to be hidden within the introns; engineered genes stripped of their introns will often produce no protein.

Perhaps most important, the concept of introns and exons forms the basis for a striking new evolutionary theory. Harvard's Gilbert has proposed that novel genes are created by shuffling exons, a mechanism of evolutionary change completely independent of mutations. Such a notion was inconceivable until Roberts and Sharp's work that summer of 1977, notes Stanford University molecular biologist Paul Berg. Adds Berg, "The full implications of [their] finding has simply become more and more profound over time."

–John Travis

Chemistry: Laurels for a Late-Night Brainstorm

Kary Mullis isn't your typical Nobel laureate. For one thing, he isn't affiliated with Harvard, or Stanford, or MIT. In fact, he isn't affiliated with any scientific institution: He works from his home in La Jolla, California. Nor does he evince the humility, amazement, and gratitude most Nobelists recount

AP

At the wave's crest. PCR inventor Kary Mullis.

as they describe getting that magic call from Stockholm.

Indeed, Mullis says he wasn't all that surprised to hear he'd won half of this year's Nobel Prize in chemistry, sharing the prize with Michael Smith of the University of British Columbia, who won for a different contribution to DNA technology (see accompanying story). "I figured they had to give it to me eventually," he says. The basis for his confidence: One night in 1983, when Mullis was working at the now defunct biotech firm Cetus Corp., he conceived the polymerase chain reaction (PCR), a method for amplifying specific stretches of DNA that has changed the face of biology and medicine.

It's hard to overstate the importance of PCR, says Gerald Joyce of the Scripps Research Institute in La Jolla. "Pick a stock superlative. Virtually everyone [in molecular biology] uses PCR in some way." Joyce's own area, test-tube molecular evolution, has blossomed thanks to PCR's capacity to home in on a few DNA or RNA molecules and amplify them into a large population. Another of today's hottest subdisciplines, the study of DNA from ancient tissues, simply couldn't exist without PCR's ability to expand traces of genetic material into quantities large enough to study, says Raul Cano, an ancient DNA researcher at California Polytechnic State University. The technique has also become indispensable in established fields such as disease diagnosis, forensic analysis, and genome sequencing.

Before PCR, obtaining enough of a specific sequence to work with from a large mass of DNA was a difficult, time-consuming job. But Mullis' invention changed all that. Its basic recipe requires a combination of three ingredients: A generous helping of DNA's four nucleotide building blocks; a polymerase enzyme that does the actual work of copying the DNA by joining the building blocks in the correct order; and two primer sequences, short DNA segments that bind to the sample at either end of the target sequence and tell the polymerase where to copy.

To get the reaction under way, the sample is heated, causing the DNA's complementary strands to separate. When the mixture is cooled, the primers find their sites on the separated strands, and the polymerase copies each target region. Repeating the cycle of heating and cooling leads to exponential growth in the number of DNA copies. Thirty cycles, lasting a few minutes each, are enough to mass produce millions of identical copies of the target sequence.

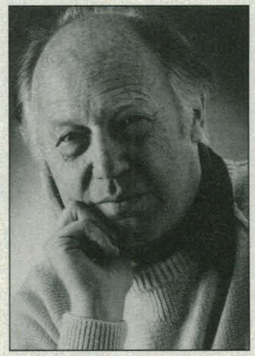
Since Mullis and his Cetus colleagues first published the technique in 1985 (*Science*, 20 December 1985, p. 1350), it's been automated and modified in so many ways that Mullis says he can no longer keep up. And work on the technique itself pales next to the science it has produced. "If you bundle all the science that's come out of PCR, that's a tremendous body of literature," says Joyce.

Still, one past Nobelist, who asked not to be named, argued that, for all its enormous impact, PCR is just a clever technical trick that doesn't have the intellectual content of Nobel-quality work. To that objection, Cano has a quick answer: "Oh yeah? Then how come I didn't think of it?"

–Tim Appenzeller

Chemistry: Changing the Landscape of the Possible

Just before 7:00 A.M. on Wednesday, 13 October, a sleepy Michael Smith of the University of British Columbia turned on the radio to hear the latest baseball scores. But instead of learning whether Atlanta or Philadelphia had inched closer to playing the Toronto Blue Jays in this year's World Series, the biochemist heard his own name preceded by the words "Nobel Prize in Chemistry."



Gene tailor. Chemistry co-winner Michael Smith.

Like co-winner Kary Mullis (see accompanying story), Smith won his laurels for developing a means of manipulating DNA molecules. Site-directed mutagenesis, Smith's innovation, enables thousands of researchers to reprogram at will a cell's DNA —and thereby change the structure of the proteins the DNA encodes. Together with the polymerase chain reaction (PCR), the DNA-amplifying method for which Mullis won his award, Smith's technique "has simply changed the landscape of the possible" in basic research and protein engineering, says protein scientist Jeremy Knowles, dean of the faculty of arts and sciences at Harvard.

Before Smith's work in the early 1980s, researchers had no way to deliberately vary the DNA that encodes a protein's amino acids sequence. The best they could do was expose cells to chemical mutagens or radiation to induce random mutations in a gene, then forage among a crowd of mutated proteins for ones that might shed light on the question at hand. Smith envisioned a way to do better, by creating specific mutations in DNA and thereby getting customized proteins.

The first step of his procedure is to splice a normal gene into the circular, single-stranded DNA of a virus. Next, a researcher (now more likely a machine) chemically synthesizes a short segment of DNA that is an exact complement of the normal gene sequence except at a single amino-acid coding site. The segment is allowed to bind to the normal gene, forming a short region of double-stranded DNA. A polymerase enzyme completes the second strand, and the double-stranded product is inserted into the genome of a bacterium. As the microbes grow, they use both the normal and the mutated versions of the gene as templates for synthesizing normal and mutated protein molecules, which can then be compared.

Thanks to that scheme, says structural biologist Brian Matthews of the University of Oregon, "if you believe that a certain amino acid has a key function in a protein, then you can test that prediction by reordering the amino acids." Besides spurring basic research, the ability to make such alterations has opened the way to tailoring enzymes to make them more stable under industrial conditions. It has even raised the prospect of redesigning proteins to have entirely new functions for industry or medicine. "Mike has provided a tool that is used by everybody in protein engineering and molecular biology," says Jim Wells of Genentech Inc.

That includes Smith, who continues to use the technique to study how particular amino acids affect the activity of cytochrome C (a protein involved in cellular respiration) and myoglobin (an oxygen storage protein). Given the technique's impact, should he have applied for a patent? "It never occurred to me," he says. But Smith has no regrets, he says; the scientific profits have been more than enough.

–Ivan Amato

Physics: A Prize for Patient Listening

Alfred Nobel never set up a prize for astronomy, but he did leave astronomers a back door to Nobel glory: the Nobel Prize in physics. And this year, that door opened for Princeton astronomers Joseph Taylor and Russell Hulse. Their radio observations of an orbiting pair of superdense stars during the 1970s yielded what physicists consider one of the most striking confirmations of general relativity, Einstein's theory of gravity.

Going on nothing but the timing of radio blips from one of the two invisible objects, Taylor and Hulse, who was then Taylor's graduate student, were able to con-

Split-second timing. Russell Hulse *(left)* and Joseph Taylor, who found and studied a binary pulsar.

struct a complete portrait of the pair, including their mass, separation, and orbital period. They also measured a minuscule shrinkage in the orbit—strong indirect evidence, physicists believe, that the pair is dissipating energy by emitting gravitational waves. These ripples in spacetime are a long-sought consequence of general relativity, and their existence would provide what gravitation expert Kip Thorne of the California Institute of Technology calls "the most important of all tests" of the theory.

Hulse and Taylor, then at the University of Massachusetts, Amherst, found the unusual binary while combing the skies for pulsars—radio-emitting collapsed stars, or neutron stars. By 1974, when they made their Nobel find, Taylor and Hulse had discovered dozens of "ordinary" pulsars, which emit their radio pulses with clockwork regularity as they spin several times a second. But the new pulsar's emissions weren't quite uniform. The interval between pulses averaged .06 second, but it shortened and lengthened slightly over a regular, 8-hour schedule.

The astronomers concluded that the pulsar had to be moving toward and away from Earth, resulting in a Doppler shift in its pulses, like that of a train whistle as it approaches and recedes. And that implied that the pulsar is orbiting a companion object. Aside from this regular variation, the timing of the pulses was so perfect that the other body had to be a compact neutron star as well, with no atmosphere or internal dynamics to throw off the clockwork timing.

Taylor and Hulse quickly realized that the binary pulsar was much more than an astronomical curiosity. Within a couple of weeks after the discovery, says Taylor, "it was clear we were going to see relativistic effects." The powerful, shifting gravitational fields of the whirling neutron stars would magnify the subtle effects of relativity, and their enormous density would prevent exchanges of gas or tidal shifting from contaminating those effects.

Seizing the opportunity, Hulse and Taylor kept timing the pulsar's blips with the world's best atomic clocks. Within a couple of years the two were able to show that the system manifests several of the effects predicted by general relativity, including a bending of the path of radio waves from the pulsar as it passes behind the other neutron star and a precession in the system's axis of rotation. But "the real zipper," in the words of Massachusetts Institute of Technology (MIT) physicist Rainer Weiss, was the subtle shortening of the 8-hour orbital period.

Something is sapping energy from the orbiting bodies—and in 1978 Hulse and Taylor showed that the loss exactly matches what would be expected if the system is emitting gravitational waves. Einstein predicted that such waves should spill into space from certain massive, oscillating bodies. And though no one has detected gravitational waves directly, Thorne and other physicists consider Hulse and Taylor's results to be the most convincing indirect evidence for them.

Colleagues in radio astronomy also admire the painstaking work required to tease out this subtle Einsteinian effect. Hulse and Taylor had to measure a shortening in the binary pulsar's orbital period amounting to just 75 millionths of a second per year. "Taylor is such a superb experimentalist," says Thomas Gold of Cornell University, a founder of the Arecibo radio observatory in Puerto Rico, where the pulsars and companion were found and studied. Adds MIT's Weiss, "All they had were pulses—there's nothing to be seen with your eyes. From being careful and patient they learned so much."

–Faye Flam

Economics: A Subdiscipline Comes in From the Cold

Many a Nobel Prize is given for work that falls squarely in the mainstream. But sometimes the prize goes to researchers who have labored on the fringe, trying to turn their area into a new mainstream. That's the case for this year's Nobel Prize in Economics, awarded to Robert Fogel of the University of Chicago and Douglass North of Washington University in St. Louis. For decades, the two researchers, working independently, struggled to revitalize a backwater field: economic history.

"These people came into history carrying the weapons of science, such as math, statistics, and computers," says James Heckman, an economist at the University of Chicago. "And like those bringing gunpowder to Europe, they were not always liked." Both historians and economists were wary of this hybrid endeavor. But Fogel and North persisted, and their work, according to the Nobel citation, "deepened our knowledge and understanding…as to how, why, and when economic change occurs."

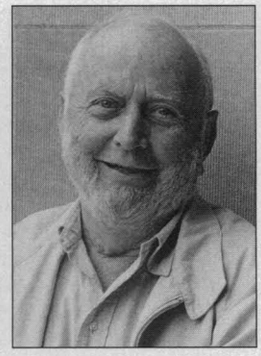
For North, a theorist at heart, the past is primarily a testing ground for hypotheses about the forces that propel economic development. Contrary to what many of his colleagues have proposed, his studies have convinced him that technical innovations by themselves aren't enough to drive economic development; institutions, such as the judiciary and guilds, often play the key role. The surge in the productivity of ocean shipping during the 19th century, North showed in 1968, owed more to efforts to reduce piracy and improve emergency services than to technical improvements.

More recently, North has studied the institutional factors that make countries rich or poor—a burning issue today. Says John Nye of Washington University, "North's work is more relevant than ever with the end of the cold war. While many neoclassical economists' advice has been limited to 'Let the market work,' North has been adamant in exploring the institutional context under which markets can function properly…."

Fogel, though less a theorist than a meticulous empiricist, has reached similar conclusions about the complex forces that drive economic change. His early work disputed the belief that the advent of the railways single-handedly spurred U.S. economic growth in the 19th century. Actually, he found, the stimulus came from a host of smaller technical changes. Fogel has also concluded that economic forces alone do not determine economic history. In his 1974 book *Time on the Cross*, Fogel argued that slavery, despite its inhumanity, was economically efficient, and it could not have ended through market forces. "Slavery," he wrote, had to end "through political intervention, based on an evolving American ethic against slavery."

That conclusion unleashed a storm of controversy, since many historians thought slavery was an economic dead-end. Fogel responded to his critics with a four-volume work, *Without Consent or Contract*, packed with data substantiating his claim. That doggedness is typical, say colleagues. "He moves slowly, surely, and like a tank, he grinds down everything in his path," says Heckman. That's what it takes to move from the fringe to center stage at Stockholm.

–Anne Simon Moffat



History buffs. Economics nobelists Robert Fogel *(left)* and Douglass North.