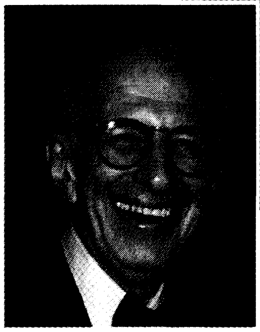
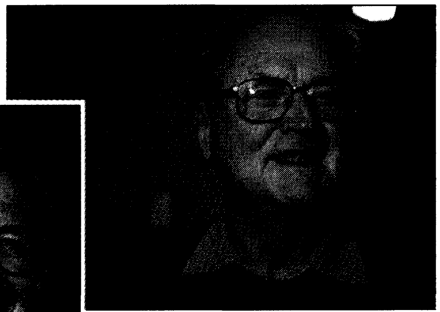
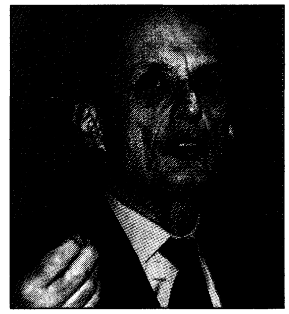
PHYSIOLOGY NOBEL

Celebrating the Synapse

Arvid Carlsson first started thinking that he might win a Nobel Prize nearly 40 years ago. Since then, he says, "I've been up and down about it many times." Carlsson need not have fretted. His pivotal discovery—that dopamine is a key neurotransmitter in the brain—not only led to treatments for Parkinson's disease and schizophrenia, but also sparked a revolution in neuroscience that has helped keep the field on a constant high ever since.







Neuro trio. Eric Kandel, Arvid Carlsson, and Paul Greengard (*clockwise from left*).

Last week, the Nobel Assembly recognized those achievements, awarding the Nobel Prize in physiology or medicine to Carlsson of the University of Gothenburg in Sweden and to two other pioneers in the study of nerve cell communications: Paul Greengard of Rockefeller University in New York City, who figured out how dopamine and other neurotransmitters trigger their target neurons when they bind at the synapse, the junction between two nerve cells; and Eric Kandel of New York's Columbia University, who built on these insights to demystify some aspects of learning and memory.

"This prize is really a celebration of the synapse," says neuroscientist Corey Goodman of the University of California, Berkeley. He and others applaud the Nobel committee's decision to honor nearly a half-century of neuroscience research. "These people are all towering figures" in the field, says neurobiologist Charles Stevens of the Salk Institute for Biological Studies in La Jolla, California.

The story of this year's prize began in the 1950s, when Carlsson, now 77, overturned conventional wisdom by proving that dopamine—once thought to be merely a precursor in the synthesis of the neurotransmitter norepinephrine—is an important nervous system messenger in its own right. In one key experiment, he and his colleagues gave rabbits a drug that depletes norepinephrine in the brain, putting the animals into a temporary stupor. Carlsson found that the rabbits could be roused with injections of L-dopa, which the brain converts to dopamine. According to the then-prevailing view, the dopamine should have been converted to norepinephrine. But he found only dopamine in the animals' brains—indicating that it was responsible for the rabbits' recovery.

Carlsson and others later discovered that Parkinson's disease, which causes rigidity and tremors, results from degeneration of dopamine-producing neurons in a brain region involved in movement control. That finding led to the use of L-dopa as a therapy for Parkinson's patients. Further studies on the connections between neurotransmitter levels and mental states spawned a wealth of drugs, including Prozac, that fight psychosis and depression.

In the 1960s, Greengard, 74, took Carlsson's insights several steps further by exploring how dopamine, norepinephrine, and serotonin trigger responses in their target neurons. Back then, Greengard says, most neuroscientists believed that nerve transmission was purely electrical, propagated by the flow of charged ions across nerve cell membranes. But he showed that this is only half of the story.

In most neurons, Greengard found, the neurotransmitters exert their effects biochemically, by triggering a so-called second messenger inside the target cells. This in turn activates an enzyme that adds phosphate groups to cellular proteins, thus setting off a chain of events that alter nerve cell properties—for example, heightening or damping sensitivity to electrical stimulation. To date, Greengard and his colleagues have identified more than 100 brain proteins phosphorylated as a result of neurotransmitter activity, including one that serves as a kind of master control switch for dopamine.

The link between phosphorylation and nerve cell signaling inspired the research of Kandel, 70, into how the brain learns and remembers. Kandel, who started his career as a psychiatrist, began dabbling in learning and memory research as a postdoc at the National Institutes of Health in the late 1950s. But although his work there recording electrical impulses from the hippocampuses of cats resulted in some "very nice papers," Kandel says, he wanted a system that was easier to work with. So he went to Paris to study with Ladislav Tauc, an expert on the sea slug *Aplysia*, famous for its giant neurons. "With *Aplysia*, you can just record from those cells until the cows come home," Kandel says.

Over the following years, Kandel demonstrated that the responses of *Aplysia*'s nerve cells to various stimuli—such as touching the animal's tail or giving it an electrical shock—were amplified according to the strength and duration of the stimuli. These heightened responses could last for days or weeks, thus demonstrating a form of learning and memory. In general, weak stimuli gave rise to short-term memory, and stronger stimuli to long-term memory.

Kandel, sometimes in collaboration with Greengard, went on to show that short-term memory is created by means of phosphate addition to proteins that make up the pores in the cell membrane that calcium and other ions involved in nerve transmission flow through. Long-term memory, he found, forms when stronger stimuli trigger the synthesis of new proteins that change the shape of the synapse and its sensitivity to further stimuli.

This finding helped solved a long-standing puzzle: why protein synthesis is necessary for long-term memory but not for short-term memory. It was also the culmination of decades of work that began with Carlsson's pioneering discoveries in the 1950s. When asked how winning the Nobel Prize might change their lives, all three recipients told *Science* they hoped the impact would be minimal. "I will try very hard not to let it affect my life," says Kandel. "I already like my life."

—MICHAEL BALTER

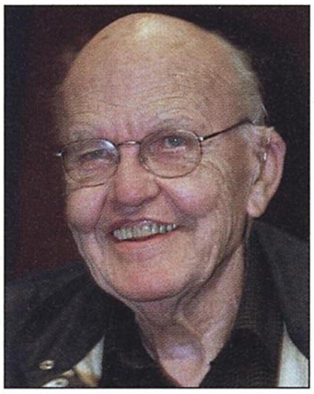
PHYSICS NOBEL

Achievements Etched In Silicon

Silicon, rather than gold, might be an appropriate material for this year's Nobel Prize in physics. For it was with silicon that the three recipients—Jack Kilby of Texas Instruments in Dallas; Herbert Kroemer of the University of California, Santa Barbara; and Zhores Alferov of the A. F. Ioffe Physico-Technical Institute in St. Petersburg, Russia—made their crowning achievements. Computers, cell phones, and CD players rely on technology they made possible.

CREDITS: (CLOCKWISE, FROM LEFT) E. BAILEY/AP; A. ERIKSSON/AP/PRESSENS BILD; D. KARP/AP

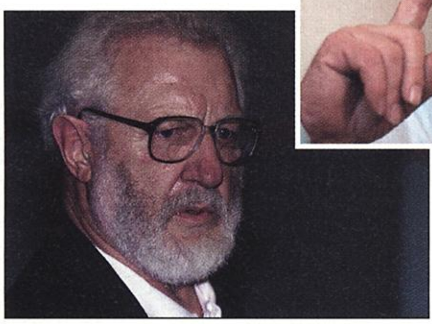
Silicon technology has come a long way. In late 1947, scientists at Bell Laboratories invented the transistor, ushering in the computer age. John Bardeen, Walter Brattain, and William Shockley won the 1956 Nobel Prize for the invention, but their transistor was not ideal. Although it was much smaller and more reliable than the vacuum tubes it replaced, manufacturers still had to solder thousands of transistors and other components to a circuit board to construct even the most rudimentary computers. "By that time people could visualize electronic equipment that couldn't be built—it was too expensive, too bulky, and too unreliable," Kilby recalls.

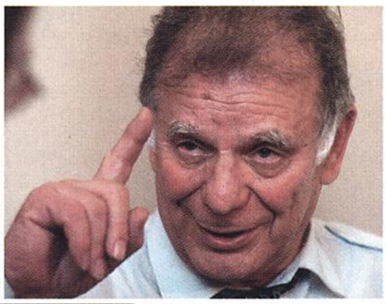


Integrator. Jack Kilby produced the first integrated circuit.

In 1958, Kilby was stuck in the laboratory; just hired by Texas Instruments, he hadn't earned the vacation time to get away for the summer. But Kilby made good use of the extra time in the lab: He came up with a radical solution to the assembly problem.

Instead of taking lots of individual transistors and soldering them together, Kilby put all the components of a circuit on a single wafer of semiconducting crystal such as germanium or silicon. He did this by taking a wafer of germanium, covering bits of it with black wax, and then exposing the wafer to acid, so that areas that weren't protected by the wax were etched away. In this way, he carved transistors, resistors, condensers, and other elements on the same wafer and out of the same materials—all layered and wired on one crystal. This "integrated circuit" avoided the labor problems, space constraints, and quality-control issues that plagued circuit boards assembled from individual transistors. Kilby and a competitor, the late Robert Noyce of Intel, are credited with inventing the integrated circuit that put the computer revolution in high gear.





Souped-up silicon. Herbert Kroemer and Zhores Alferov (*inset*) saw the way to high-speed solid state components.

CREDITS: (TOP TO BOTTOM) T. SHARP/AP; D. LOVETSKY/AP; P. KLEIN/AP

Kroemer wins his Nobel Prize for refining the basic transistor that made it faster and more efficient. The key to this invention lies in modifying the flow of negatively charged electrons and positively charged "holes"—spaces vacated by electrons—through semiconductors. Though electrons carry the charge, the holes act as if they were particles that carry a positive charge.

In an ordinary transistor, when electrons flow in one direction, holes swim upstream in the opposite direction. Unfortunately, the bigger the reverse flow of holes, the less amplification the transistor gives—the less powerful it is. The so-called heterojunction bipolar transistor solves this problem by using layers of two complementary semiconductors (such as gallium arsenide with aluminum gallium arsenide), whereas traditional transistors used just one (such as silicon). Electrons can cross from one semiconductor layer to the other easily, but holes cannot (or vice versa, depending on the configuration). By doing this, "you prevent holes from flowing in the reverse directions—they run into a potential barrier," explains Jim Merz, a physicist and vice president at Notre Dame University in Indiana. "This was Kroemer's idea; he realized that it had huge implications."

Better yet, Kroemer realized—as did Alferov—that these heterogeneous semiconductors could be turned into lasers. By arranging materials in the proper fashion, it's possible to create a trap for electrons and holes—a region where they can flow in but can't flow out. When an electron and a hole meet inside this trap, they recombine, releasing light. This light, in turn, incites more trapped electrons and holes to recombine. It's just like a traditional laser, but it can be made out of semiconductors.

Kroemer and Alferov's brainstorm led to the development of radio satellites, base stations for mobile phones, fiber optic cables, and CD players, notes semiconductor laser researcher Al Cho of Lucent Technologies' Bell Laboratories in Murray Hill, New Jersey. "I think they certainly are pioneers."

–CHARLES SEIFE

CHEMISTRY NOBEL

Getting a Charge Out of Plastics

Polymers generally make good insulators: Witness the plastics shrouding the wires in your home. But this year's Nobel Prize in chemistry was awarded to a trio of researchers—Alan Heeger of the University of California, Santa Barbara; Alan MacDiarmid of the University of Pennsylvania in Philadelphia; and Hideki Shirakawa of the University of Tsukuba in Japan—for discovering that plastics can be made electrically conductive. The discovery paved the way for revolutionary applications such as full-color displays for cellular phones and plastic electronics for computerized merchandise, as well as still-futuristic hopes of computing with molecules and creating cheap, large-area solar cells.

The initial discovery of electrically conductive plastics stemmed from a wonderful bit of serendipity. In an experiment in the early 1970s, one of Shirakawa's students accidentally added excess catalyst to a brewing batch of plastic called polyacetylene. The result was a shiny silvery film. Shirakawa told MacDiarmid of his discovery during a visit to Kyoto University in 1975. "When MacDiarmid saw it, he was very surprised," says Shirakawa.

It turned out MacDiarmid and Heeger—who was also at the University of Pennsylvania at the time—had been experimenting with metallic-looking films from polymers made from inorganic building blocks. They were trying to learn more about the changes that take place as materials change from insulators to metals. The inorganic polymers were scientifically interesting because they showed hints of this change, but they couldn't be modified easily like organic polymers, says Heeger. So when MacDiarmid returned to Pennsylvania and told Heeger of Shirakawa's work, "I said, 'This is what we're looking for,' " recalls Heeger.

MacDiarmid invited Shirakawa to visit the University of Pennsylvania, and the researchers quickly set about modifying the polymers and testing the results. In one case, they used an iodine vapor to oxidize the film, a treatment they knew could change the film's optical properties. But that was the least of the changes: The conductivity shot up by 10 million times. Polyacetylene, like other conducting polymers discovered since, is a chainlike molecule with alternating double and single bonds. When excess charges are added to the molecule—as happens during oxidation—these charges can then hop along the alternating bonds with