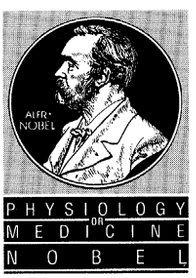
Cancer Gene Research Wins Medicine Nobel

Two U.S. scientists are cited for work that is helping to unravel the genetic changes that can lead to cancer



VERY FEW NOBEL PRIZES have been awarded for research directly related to cancer. But this year's Prize for Physiology or Medicine marks an exception. It has been won by J. Michael Bishop and Harold Varmus of the University of California, San Francisco, who were cited for their 1976 discovery that normal cells contain genes that can cause cancer if they malfunction.

Before this discovery, cancer-causing genes, called oncogenes, had been found only in certain viruses that cause cancers in animals. As a result, many researchers were skeptical about whether the viral oncogenes had anything to do with human cancers.

But that all changed when Bishop and Varmus found that the viral oncogenes are derived from cellular genes that the viruses had apparently picked up from an infected cell at some point in their evolution. "The real breakthrough was not the discovery of viral oncogenes but the finding that these were altered normal cell genes," says virologist Howard Temin of the University of Wisconsin in Madison, whose own research won him a share of the 1975 medicine prize.

The award touched off an international controversy, however, when Dominique Stehelin, a French researcher, protested because he had not been granted a share of the prize (see box). Stehelin participated in the work that led to the award.

Whatever the merits of that claim, it is clear that the work of the Bishop-Varmus group has had a major impact on efforts to understand the genetic basis of cancer. Since their 1976 discovery, researchers have identified nearly 50 cellular genes with the potential of becoming oncogenes.

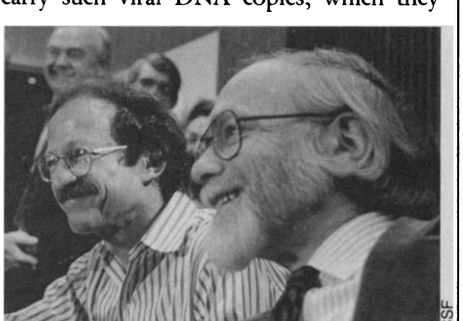
The availability of those genes is now making it possible to dissect the biochemical pathways leading to cancer development, possibly suggesting better ways of preventing or treating cancer. The oncogene work is already paying off clinically in helping physicians predict how patients with certain cancers will fare. The presence of a particular oncogene abnormality in a breast cancer, for example, means that the patient from whom it was taken is likely to have a poor prognosis and needs aggressive therapy after surgery to prevent a cancer reoccurrence.

The two new laureates started on their road to Stockholm back in 1970 when Varmus became a postdoctoral fellow in the Bishop group. "I ran into Mike Bishop almost by accident when I went to San Francisco," Varmus recalls. "But Mike and I hit it off right away."

Both researchers were intrigued by a group of viruses, known as the retroviruses, that cause cancers in animals. They focused in particular on Rous sarcoma virus, which produces tumors called sarcomas in chickens. It can also cause cultured cells to become malignant. "I remember being tantalized by how you could infect normal [cells] with this virus and within 24 hours, they looked like cancer cells," Bishop says.

Despite the clear carcinogenic effects of Rous sarcoma virus and other retroviruses in animals and cultured cells, an intensive search in the early 1970s failed to turn up any evidence that infections by retroviruses caused human cancers. This added to the skeptics' argument that viral oncogenes weren't relevant to human cancers. However, Robert Huebner and George Todaro, who were then at the National Cancer Institute in Bethesda, Maryland, had proposed a way in which retroviruses might contribute to human cancer development, even if not by direct infection.

They had suggested that all cells might carry such viral DNA copies, which they called "proviruses," as the result of an infection early in evolutionary history. The viral DNA might then lurk inactive and silent in the genome until some event, such as exposure to a chemical carcinogen, turned on the viral genes, thereby triggering development of a cancer.



Smiles in San Francisco. *Harold Varmus (left) and Michael Bishop meet the press.*

Bishop and Varmus set out to determine whether the provirus theory was correct—and in so doing made their key discovery. By the mid-1970s, other investigators had found that the cancer-causing ability of Rous sarcoma virus could be attributed to just one of the four genes in the viral genome. This cancer-causing gene, or oncogene, was named *src* for sarcoma. The identification of the *src* gene provided a tool, Bishop says, that could be used to probe cells to see if they contained silent copies of cancer-causing viral DNAs.

Bishop and Varmus, with Stehelin and postdoctoral fellow Deborah Spector, found that they could detect *src* gene DNA in cells from several bird species and from mammals as well. At first glance this seemed to support the provirus theory. But several lines of evidence indicated that the *src* gene that they

Controversy Over Nobel

Controversies about scientific prizes are nothing new, but they are rarely as public as the one sparked by French researcher Dominique Stehelin over this year's Nobel Prize for Physiology or Medicine. Backed by other French scientists and senior government officials, Stehelin has complained bitterly because he did not share the prize, which was awarded jointly to J. Michael Bishop and Harold Varmus of the University of California, San Francisco.

Bishop and Varmus were cited "for their discovery of 'the cellular origin of retroviral oncogenes.' " And that is what has raised Stehelin's ire. "I would have said nothing if [the citation] hadn't been so narrowly defined," he told *Science*.

Stehelin is now a researcher with the Centre National de la Recherche Scientifique at the Pasteur Institute in Lille. But from 1972 to 1975, he worked in Bishop's laboratory. While there, he carried out experiments showing that the *src* oncogene originally identified in Rous sarcoma virus is in fact a chicken cell gene that the virus had picked up from an infected cell at some point in its history.

That much is not in dispute. In telephone interviews with *Science*, both Bishop and Varmus credited Stehelin for perform-

ing those experiments. But what is in dispute—and it is a recurring issue when it comes to awarding scientific prizes—is who should get the primary credit: the principal investigators who guided the laboratory's research or the more junior scientists who did the experiments?

Both Bishop and Varmus pointed out that other researchers in their laboratories had also contributed to the work that won the Nobel Prize. "Dominique played a major role in one piece of the story, but it was not the whole story, which developed over the course of years," Varmus says. Ramareddy Guntaka, for example, had begun the work on the probe needed to detect the cellular *src* gene before the project was assigned to Stehelin. And Deborah Spector, now at the University of California in San Diego, performed the experiments showing that the *src* gene is also present in mammalian cells.

But French officials evidently think Stehelin's claims have merit. According to the Reuters news agency, Hubert Curien, the minister for research and technology, has joined a chorus in France protesting that Stehelin should have won the award too.

Will any of this change the prize committee's mind? Definitely not. "It is our opinion that [Bishop and Varmus] are the key persons in the discovery," says Jan Lindsten, secretary of the Nobel medicine committee. ■ **J.L.M.**

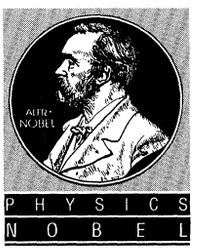
were detecting in cells was not of viral origin at all, but was instead a cellular gene. That was a surprise. "There were a lot of people around who were telling us we were looking at an artifact," Bishop says.

But the San Francisco group had made no mistake. Subsequently, many investigators, including Bishop and Varmus, established that the oncogenes found in other cancer-causing retroviruses are also of cellular origin. And those genes have since been cloned and sequenced and their identities established beyond doubt.

In their normal state, the cellular genes, which are called proto-oncogenes, control cell growth and development. But the sequencing also revealed that when the proto-oncogenes were picked up by the retroviruses, they underwent changes that allowed them to go awry, causing the uncontrolled growth and other abnormalities of cancer cells. More recently, researchers have evidence that chemical carcinogens can also convert proto-oncogenes to active oncogenes. In fact, Bishop describes the proto-oncogenes as "the keyboard on which carcinogens play." ■ **JEAN L. MARX**

Basic Measurements Lead to Physics Nobel

Their work on atomic properties led to atomic clocks, magnetic resonance imaging, and verifications of quantum mechanics



WHEN THE NOBEL PRIZE COMMITTEE divided the 1989 physics prize into two halves last week, it may have had two very different motives. On the surface the committee provided a single rationale: to honor pioneering work over the past 30 years that vastly improved the measurements of fundamental atomic properties.

But the accomplishments being saluted were of two very different kinds. One was seminal, Nobel-quality work in a single field, the other more of a lifetime achievement award.

Half of the $469,000 prize went to Norman Ramsey of Harvard University, who invented the "separated oscillatory fields method" for measuring the differences between atomic energy levels. This method, the Nobel committee noted, was essential to developing today's superaccurate atomic clocks, which allow time measurements of an accuracy of about 1 part in 10 trillion. Ramsey was also cited for his work on the hydrogen maser, the microwave analogue of the laser.

The other half of the award was divided between Hans Dehmelt of the University of Washington and Wolfgang Paul of the University of Bonn in West Germany for their development of ion trap techniques. Their work has allowed researchers to isolate individual atoms and particles and perform exacting measurements on them.

Comparing the two halves of this year's award, Paul and Dehmelt's development of ion traps is undoubtedly "Nobel quality" work in and of itself, while Ramsey's half of the prize may have been more a recogniion of an outstanding physics career.

Paul, 76, performed the first experiments on trapping atoms and ions in the 1950s. He showed that it is possible to use a hexapole magnetic field to focus a beam of atoms and later developed a way to separate ions of different masses that ultimately evolved into the now widely used a quadrupole mass spectrometer. Paul also invented a way to hold ions in a small area using only radio-frequency radiation. This "Paul trap" or "radio-frequency trap" was the first ion trap and is still one of the most commonly used.

Where as Paul made his reputation in developing various machines for studying atomic properties, Dehmelt is better known for pushing the machines to their limit in measuring those properties. Robert Van Dyck, who went to the University of Washington in 1973 to work with Dehmelt, characterizes his mentor's career as devoted to creating an ideal system in which to perform atomic measurements. Each improvement in the ion traps was aimed at achieving "a single particle without unwanted interactions, suspended in an environment we could control," Van Dyck said.

Dehmelt, 67, lived in Germany until 1952, when he moved to the United States. In 1955, he developed the "Penning trap," which uses a strong magnetic field and a weak electric field to hold ions. He used the Penning trap to study electrons with the goal of measuring the electron "*g*-factor"—essentially the ratio of the magnetic and angular momenta of the electron.

In 1973, working with Van Dyck, Dehmelt finally succeeded in isolating a single electron in the Penning trap, and 2 years later he invented a way to cool the electron so as to improve the accuracy of measurements on it. This, Van Dyck said,

Physics laureates. *From left, Norman Ramsey, Harvard; Wolfgang Paul, University of Bonn; Hans Dehmelt, University of Washington.*