Essays of an Information Scientist: Journalology, KeyWords Plus, and other Essays, Vol:13, p.125, 1990 Current Contents, #16, p.3-10, April 16, 1990

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The 1989 Nobel Prize in Physiology or Medicine Is Awarded to J. Michael Bishop and Harold E. Varmus for Their Contribution to Cancer Research

Number 16 April 16, 1990

This essay examines the work of J. Michael Bishop and Harold E. Varmus, recipients of the 1989 Nobel Prize in physiology or medicine for the discovery of the cellular origin of retroviral oncogenes. The award is entirely consistent with their citation records as well as their rankings in ISI® listings of most-cited scientists. The laureates' highly cited papers are examined, as are pertinent research fronts. Also discussed is the controversial protest by their former colleague Dominique Stéhelin.

The 1989 Nobel Prize in physiology or medicine was jointly awarded to J. Michael Bishop and Harold E. Varmus, both from the University of California, San Francisco (UCSF), for their revolutionary discovery that normal cells contain genes that can cause cancer if they are altered. This discovery was first published in a 1976 landmark article in *Nature*.[1]

The choice of Bishop and Varmus was hardly a surprise to Nobel forecasters.[2] Indeed, these two scientists had already won the Lasker Basic Medical Research Award in 1982 and the Gairdner Award in 1984, two highly prestigious awards that have frequently anticipated the Nobel.

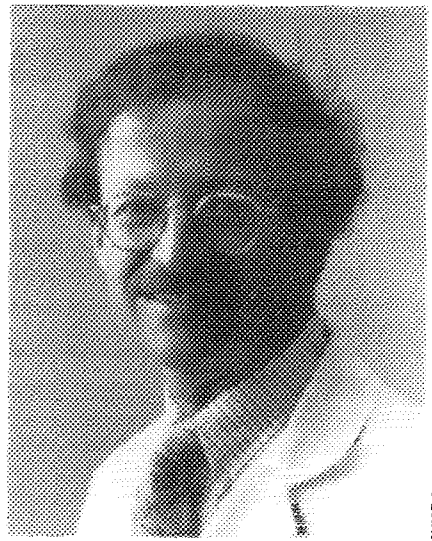
If citation history is an indicator of Nobel-class research, and it has been in the past, these two scientists are surely of that caliber. Both were on our list of the 200 most-cited scientists between 1973 and 1984. Bishop's work has been cited over 10,000 times, making him the 24th most-cited scientist in the ISI® database for 1973-1984; Varmus is ranked 55th, with over 8,700 citations.[2] Table 1 lists 29 papers published by Varmus and Bishop, either individually or together, that have been cited over 150 times.

Americans have received the majority of Nobel Prizes in medicine or physiology—of 46 recipients since 1970, 30 have been US citizens. However, few scientists in the award's 88-year history have received a Nobel Prize for research directly related to cancer. Peyton Rous, for example, Rockefeller Institute, New York, was awarded the prize in 1966 for discovering the first known cancer-causing virus, now known as the Rous sarcoma virus. However, as sociologist Harriet Zuckerman, Columbia University, New York, points out in her book *Scientific Elite*, Rous had to wait 55 years for this recognition.[3] (p. 47) David Baltimore, then at the Massachusetts Institute of Technology, Cambridge, now president-designate, The Rockefeller University, along with Renato Dulbecco, director, Salk Institute of Biological Studies, La Jolla, California, and Howard Temin, McArdle Laboratory of Cancer Research, University of Wisconsin, Madison, shared the 1975 prize for their studies of tumor virus replication.

While the significance of the research recognized by the Nobel committee is unquestioned, the decision to limit recognition to Bishop and Varmus has been protested by one of their former coauthors—Dominique

UCSF/David Powers

J. Michael Bishop



UCSF/David Powers

Harold E. Varmus

Table 1: Harold E. Varmus's and J. Michael Bishop's works cited over 150 times. Data are taken from the *SCI*®, 1945-1988. A=number of citations. B=bibliographic data.

A	B
1,125	**Bishop J M.** Cellular oncogenes and retroviruses. *Annu. Rev. Biochem.* 52:301-54, 1983.
449	**Levinson A D, Oppermann H, Levintow L, Varmus H E & Bishop J M.** Evidence that the transforming gene of avian sarcoma virus encodes a protein kinase associated with a phosphoprotein. *Cell* 15:561-72, 1978.
435	**Stéhelin D, Varmus H E, Bishop J M & Vogt P K.** DNA related to the transforming gene(s) of avian sarcoma viruses is present in normal avian DNA. *Nature* 260:170-3, 1976.
427	**Varmus H E.** The molecular genetics of cellular oncogenes. *Annu. Rev. Genet.* 18:553-612, 1984.
421	**Bishop J M.** Viral oncogenes. *Cell* 42:23-38, 1985.
390	**Bishop J M.** The molecular genetics of cancer. *Science* 235:305-11, 1987.
368	**Varmus H E.** Form and function of retroviral proviruses. *Science* 216:812-20, 1982.
328	**Bishop J M.** Retroviruses. *Annu. Rev. Biochem.* 47:35-88, 1978.
321	**Shank P R, Hughes S H, Kung H F, Majors J E, Quintrell N, Guntaka R V, Bishop J M & Varmus H E.** Mapping unintegrated avian sarcoma virus DNA: termini of linear DNA bear 300 nucleotides present once or twice in two species of circular DNA. *Cell* 15:1383-95, 1978.
293	**Payne G S, Bishop J M & Varmus H E.** Multiple arrangements of viral DNA and an activated host oncogene in bursal lymphomas. *Nature* 295:209-14, 1982.
266	**Hughes S H, Shank P R, Spector D H, Kung H F, Bishop J M, Varmus H E, Vogt P K & Breitman M L.** Proviruses of avian sarcoma virus are terminally redundant, co-extensive with unintegrated linear DNA and integrated at many sites. *Cell* 15:1397-410, 1978.
263	**Oppermann H, Levinson A D, Varmus H E, Levintow L & Bishop J M.** Uninfected vertebrate cells contain a protein that is closely related to the product of the avian sarcoma virus transforming gene (*src*). *Proc. Nat. Acad. Sci. USA* 76:1804-8, 1979.
227	**Bishop J M.** Enemies within: the genesis of retrovirus oncogenes. *Cell* 23:5-6, 1981.
219	**Payne G S, Courtneidge S A, Crittenden L B, Fadly A M, Bishop J M & Varmus H E.** Analysis of avian leukosis virus DNA and RNA in bursal tumors: viral gene expression is not required for maintenance of the tumor state. *Cell* 23:311-22, 1981.
216	**Varmus H E, Vogt P K & Bishop J M.** Integration of deoxyribonucleic acid specific for Rous sarcoma virus after infection of permissive and nonpermissive hosts. *Proc. Nat. Acad. Sci. USA* 70:3067-71, 1973.
215	**Stéhelin D, Guntaka R V, Varmus H E & Bishop J M.** Purification of DNA complementary to nucleotide sequences required for neoplastic transformation of fibroblasts by avian sarcoma viruses. *J. Mol. Biol.* 101:349-65, 1976.

208 **Taylor J M, Dozy A, Kan Y W, Varmus H E, Lie-Injo L E, Ganesan J & Todd D.** Genetic lesion in homozygous alpha thalassaemia (hydrops fetalis). *Nature* 251:392-3, 1974.
206 **DeLorbe W J, Luciw P A, Goodman H M, Varmus H E & Bishop J M.** Molecular cloning and characterization of avian sarcoma virus circular DNA molecules. *J. Virol.* 36:50-61, 1980.
199 **Weiss S R, Varmus H E & Bishop J M.** The size and genetic composition of virus-specific RNAs in the cytoplasm of cells producing avian sarcoma-leukosis viruses. *Cell* 12:983-92, 1977.
194 **Ringold G M, Yamamoto K R, Tomkins G M, Bishop J M & Varmus H E.** Dexamethasone-mediated induction of mouse mammary tumor virus RNA: a system for studying glucocorticoid action. *Cell* 6:299-305, 1975.
190 **Ringold G M, Yamamoto K R, Bishop J M & Varmus H E.** Glucocorticoid-stimulated accumulation of mouse mammary tumor virus RNA: increased rate of synthesis of viral RNA. *Proc. Nat. Acad. Sci. USA* 74:2879-83, 1977.
176 **Varmus H E, Quintrell N & Ortiz S.** Retroviruses as mutagens: insertion and excision of a nontransforming provirus after expression of a resident transforming provirus. *Cell* 25:23-36, 1981.
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161 **Bishop J M, Levinson W E, Quintrell N, Sullivan D, Fanshier L & Jackson J.** The low molecular weight RNAs of Rous sarcoma virus. 1. The 4S RNA. *Virology* 42:182-95, 1970.
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Stéhelin of France. Stéhelin is now director of research, National Scientific Research Center (CNRS), Pasteur Institute, Lille, France. In an open letter to the Nobel committee, he claimed that his crucial contributions to the discoveries were ignored.[4] The controversy is discussed in more detail later.

Oncogene Hypothesis

Since the Rous sarcoma virus was first discovered in 1910, scientists have been struggling to find the exact connection between tumor viruses and cancer. Some researchers theorized about gene mutation in the etiology of cancer, as did Joshua Lederberg, now president, The Rockefeller University, in a 1946 *Science* paper.[5] In 1969 George J. Todaro and Robert J. Huebner, National Cancer Institute, proposed that viral cancer genes are found in normal cells, perhaps acquired through viral infection early in evolution. These genes lie dormant until they are stimulated by carcinogenic factors, such as chemicals or radiation, at which time they convert cells to cancerous growth.[6]

To explore this hypothesis, Bishop and Varmus in the mid-1970s decided to investigate whether the cancer-causing gene of the Rous sarcoma virus, called *src*, could be found in the DNA of normal cells. Finding one gene out of the thousands found in the genome of vertebrates was a formidable task that no one had managed to accomplish, given that the gene manipulation tools available today had not yet been fully developed.

Bishop, Varmus, and their colleagues developed a DNA probe that identified only the *src* gene.[7] Using molecular hybridization, in which chains of DNA or RNA nucleic acids attach to specific nucleic acid counterparts, they found that the *src* sequences are found in the normal cells of chickens and other birds. These results were published in the 1976 *Nature* paper that

received credit from the Nobel committee.[1] Since its publication, it has been cited over 435 times and is the third most-cited paper published by Bishop and Varmus.

In later studies the *src* gene was also found in the normal cells of mammals, including humans, and in fish.[8] Subsequent work provided further confirmation that the *src* gene discovered in vertebrates was not a viral gene after all, but a cellular gene, later called a proto-oncogene.[9] Proto-oncogenes were also found to play an active role in normal cells, producing proteins necessary for cell function.[10]

Controversy

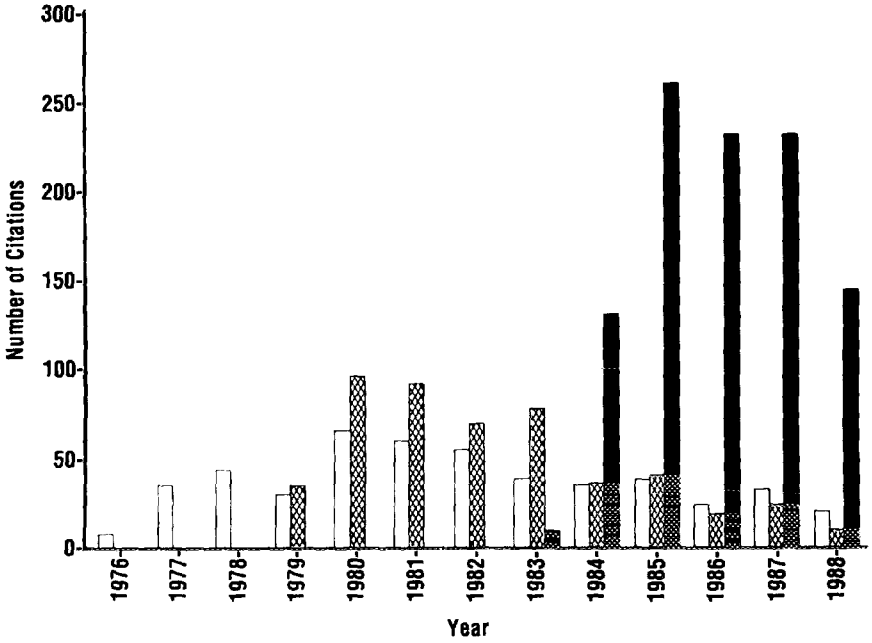
The controversial protest raised by Stéhelin stems from the key experimental work done during the mid-1970s. Stéhelin was a visiting scientist on leave from the CNRS to work in San Francisco with Bishop at the time the prizewinning work was done. He points out that he not only produced the molecular probe corresponding to the *src* oncogene, but he also performed the experiments showing that these viral oncogenic sequences had a counterpart in normal host DNA.[11] He claims further that, although Bishop as well as Varmus always acknowledged his crucial contribution in those experiments, the eight-page announcement from the Nobel committee omitted any mention of his name and did not include references to the key papers on which he appeared as first author.[1,7] In his open letter to the Nobel committee, Stéhelin requested that the committee "find a way of respecting the history of this discovery, which is in the process of being rewritten as a direct consequence of their intervention. I ask that they repair a wrong that they have done me personally and are doing themselves in deforming what was an objective reality which may no longer be so."[4]

In the wake of Stéhelin's claims, other researchers offered their own views of the work that led to the prize. One notable example was a letter to *Nature* by another former colleague of Bishop and Varmus, Ramareddy V. Guntaka, now at the Department of Molecular Microbiology and Immunology, University of Missouri, Columbia. Guntaka served as an assistant research microbiologist in the Bishop-Varmus lab in the 1970s. As he notes in his letter, he had started the work on the *src* probe under Bishop and Varmus's direction and, after obtaining favorable results, turned this task over to Stéhelin in order to pursue other projects. Implying that Stéhelin had no more claim to the prize than he did himself, Guntaka supports the decision of the Nobel committee.[12]

The Nobel committee has been inconsistent in the past in apportioning credit where many collaborators were involved. A recent editorial in *Nature* cited two interesting cases, one of them concerning Jocelyn Bell, who was excluded from the 1974 Nobel in physics despite her contribution to the discovery of pulsars, an achievement for which Antony Hewish received Nobel recognition (Hewish shared the 1974 prize with Martin Ryle). Conversely, Georges J.F. Köhler was a visiting scientist in César Milstein's laboratory at the British Medical Research Council's Laboratory of Molecular Biology in Cambridge, UK, when they unraveled monoclonal antibody technology. Yet he still shared the 1984 prize in physiology or medicine with Milstein.[13] We discussed Köhler and Milstein's work in an earlier essay.[14]

In *Scientific Elite*, Zuckerman discusses this question of "distinguishing between full-fledged scientific collaboration and supervised research assistance, between replaceable and irreplaceable contributions to prize-winning research."[3] (p. 56) She mentions the controversy surrounding the Nobel for the discovery of streptomycin, awarded to Selman Waksman in 1952. Although a court of law had determined two years earlier that Waksman's colleague Albert Schatz was a full collaborator and was entitled to a share in the royalties from the discovery, and although the case had been highly publicized in the US, the Nobel com-

Figure 1: Year-by-year citations to the most-cited works by J.M. Bishop and H.E. Varmus. White bar = Stéhelin D *et al.*, *Nature* 260:170-3, 1976. Grey bar = Levinson A D *et al.*, *Cell* 15:561-72, 1978. Black bar = Bishop J M, *Annu. Rev. Biochem.* 52:301-54, 1983.



mittee claimed not to have known of Schatz's contributions.[3] (p. 55-6)

Zuckerman also discusses the case of Oreste Piccioni, who in 1972 brought suit against Owen Chamberlain and Emilio Segrè, winners of the physics prize in 1959. Piccioni claimed that the two laureates had not acknowledged his contribution to their prizewinning discovery of the antiproton, even though they mentioned him in their original publication. Piccioni, however, unlike Bell and Schatz, lacked supporters in the scientific community. Although a judgment of dismissal was rendered in the suit, the case took over two years to settle and involved a total of 65 separate legal actions.[3] (p. 56)

Unfortunately, no matter how valid a complaint may be, an overturned decision by the Nobel committee would be unprecedented and highly unlikely; nominations, deliberations, and ultimate Nobel decisions are final and without appeal.[13] In any case, no one questions that both Bishop and Varmus are deserving of this coveted prize.

Further Research on Oncogenes

The Nobel committee announcement of the Nobel Prize in medicine or physiology states, "The explosive development of this field of research has led to the identification of more than 40 different oncogenes which direct different events in the complex signal systems that regulate the growth and division of cells. Changes in any one or more of these oncogenes may lead to cancer."[15] These proto-oncogenes are activated to cause cancer in a variety of ways, some of which are still under investigation. Proto-oncogenes can be altered by chemicals or radiation to cause cancer. But they can also malfunction when a virus infects the cell and, during its replicating process, picks up part of the proto-oncogene and puts it under viral-activated control. When the virus in-

Table 2: ISI® research fronts in which J.M. Bishop and/or H.E. Varmus are core authors. A = research-front number. B = research-front name. C = number of core papers. D = number of citing papers.

A	B	C	D
88-2673	Oncogene expression and mouse mammary tumor virus	2	249
88-2674	Oncogenes in transgenic mice	8	588
87-2657	Molecular oncobiology	3	370
87-2658	Molecular genetics of cancer	3	399
85-2623	Retroviral oncogenes and cellular proto-oncogenes	7	607
82-0102	Retroviral proviral DNA and its role in malignant transformation	5	94
82-0686	Retroviruses from mice	35	271
81-0105	Expression and integration of retroviral genes	48	481
80-1019	DNA, RNA, and tumor viruses	6	83
79-1084	Reverse transcription in viruses	16	153
78-0462	Mammary tumor viruses	12	125
78-1474	Avian tumor virus DNA synthesis	4	48
77-0028	Oncogenic viruses	112	700
77-1428	Mouse mammary tumor viruses	8	87
77-1560	Human tumor viruses	5	66
76-0303	Avian tumor viruses	6	60
76-1171	RNA tumor viruses	5	61
75-0036	Steroid hormone action and RNA	215	1,917
74-0003	RNA viruses	490	3,573
73-0002	Cancer virus	117	844

fects another cell, it inserts the kidnapped proto-oncogene into an abnormal slot in the new cell's DNA, overwhelming normal cell-growth regulation. As is noted in a 1982 *Nature* paper by G.S. Payne, also at UCSF; Bishop; and Varmus (see Table 1), a retrovirus can also insert itself within a cellular proto-oncogene domain and can cause the latter to overproduce its protein product, causing tumor growth.

The details of the oncogenic process are described by Bishop in a 1983 review article in the *Annual Review of Biochemistry*. As is seen in Table 1, this paper is the most-cited work by Bishop, receiving over 1,100 citations in the seven years since it was published. Figure 1 illustrates the yearly citations to this paper as well as to the 1976 *Nature* paper and a third work published by Bishop, Varmus, and colleagues in 1978 in *Cell* that describes the function of the protein product of the *src* gene. Citations to both the *Nature* and *Cell* papers peaked in 1980 and 1981, while Bishop's review paper peaked in terms of citations in 1985 but is still highly cited today.

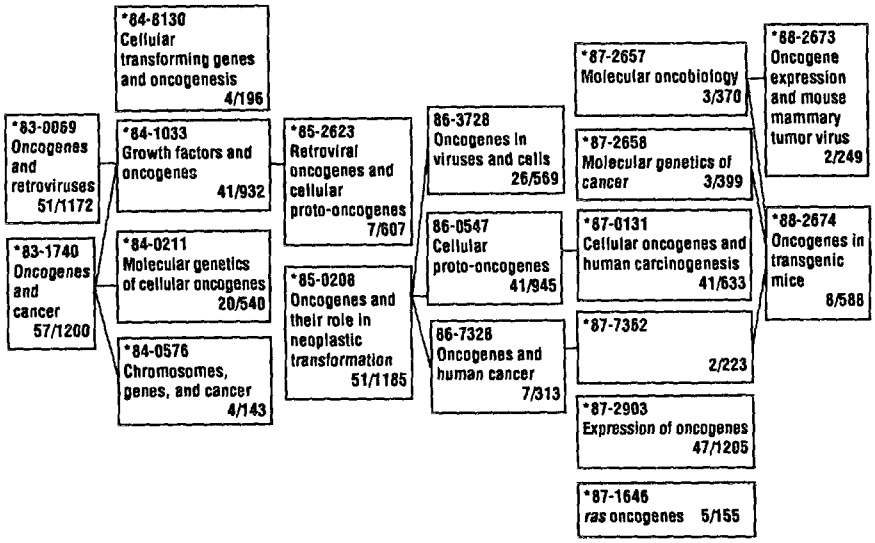
The prizewinning discovery concerning oncogenes ultimately did not bring credence to Todaro and Huebner's oncogene hypothesis but showed that oncogenes are perverted versions of fundamental genetic parts of our normal cell machinery, as summed up by Varmus in a 1982 speech:

> [Proto-oncogenes] prove not to be slumbering beasts, silent invaders of the cell's household, waiting only to be awakened by the noises of carcinogens. Instead, [proto-oncogenes] are true members of the family, multiple siblings whose lives and works are essential to the household's survival, but who are nonetheless liable to beastly behavior, hyperactivity, and other psychopathology, fatal illnesses and...kidnapping by outsiders.[16]

Bishop and Varmus

Interestingly enough, both Bishop and Varmus pursued undergraduate degrees in the liberal arts before becoming medical researchers. Bishop attended Gettysburg College, Pennsylvania, and then went on to Harvard Medical School, where he became particularly fascinated with molecular biology. In what was considered an unusual arrangement at the time, Bishop substituted full-time research for traditional course work in his fourth year of medical school. After graduation he worked as an investigator in virology at the National Institutes of Health (NIH). Bishop joined the faculty

Figure 2: Historiograph of research fronts, 1983-1988, on oncogene research. Numbers of core/citing papers are indicated at the bottom of each box. Asterisks (*) indicate research fronts in which J.M. Bishop and/or H.E. Varmus are core or citing authors.



at UCSF in 1968, where he continued studying cancer viruses.

Varmus received a degree in English from Amherst College, Massachusetts, and then went on to study seventeenth-century literature at Harvard University. Eventually, he made his way to Columbia University for his medical degree. Following that, he worked in Ira Pastan's laboratory at NIH. Varmus joined Bishop at UCSF as a postdoctoral fellow in 1970, at which time they began their prizewinning work.

Research-Front Data

Table 2 presents the research fronts in which the publications of Bishop and Varmus occur as core documents. Briefly, a research front develops when authors cite a paper to indicate its relevance to their own research. Papers that are frequently cited together, or co-cited, share common features, such as topics, results, methods, or discussions. As a result, the citing authors themselves categorize papers into subject-related clusters of research. These co-citation groups help identify research fronts. Notice that the work of Bishop and Varmus was included in three research fronts from 1977, reflecting the importance of their findings the year before. Figure 2 shows a historiograph of the winners' contributions to oncogene research between the years 1983 and 1988. Each box contains the research-front name with the numbers of core and citing papers in the lower right-hand corner. Research fronts included in this historiograph are determined by continuity of the core literature from year to year. If the same core documents are cited at the required thresholds in two adjacent years, then a "string" is established. This figure illustrates that Bishop and Varmus continue to be highly cited core authors more than a decade after their Nobel research.

Currently, Bishop and Varmus are continuing to publish studies of retroviruses, *src*, and oncogene transcriptional behavior and transformations.[17] Bishop's current work involves studies of expression and regulation of *myb* and *myc* oncogenes,[18,19] while Varmus's recently published work in-

cludes studies of ribosomal frameshifting and other processes involving the Rous sarcoma virus.[20,21]

In forthcoming essays, as is our custom, we will examine the prizewinning work by the 1989 Nobel laureates in physics: Norman F. Ramsey, Harvard University; Hans G. Dehmelt, University of Washington, Seattle; and Wolfgang Paul, University of Bonn, Federal Republic of Germany. We will also review the work of the laureates in chemistry: Sidney Altman, Yale University, New Haven, Connecticut, and Thomas Cech, University of Colorado, Boulder.

* * * * *

My thanks to C.J. Fiscus, Lisa Holland, and Christopher King for their help in the preparation of this essay.

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