

Antecedents of a Nobel prize

SIR—The award of the 1989 Nobel Prize in Medicine and Physiology to Drs J. Michael Bishop and Harold E. Varmus has ended up in a controversy raised by Dr Dominique Stéhelin. As an author of one of the two papers and one who worked for the first six months on this project, I am well placed to describe the events leading to that masterpiece work. I record here the relevant chronology as I know it so that the scientific community can judge that the prize was properly awarded.

I joined Bishop's laboratory on 4 January 1973 as an assistant research microbiologist. Stéhelin had preceded me by a few months and was working on characterizing polysome-associated virus-specific mRNA. Very soon, Stéhelin and I became close friends and began to exchange views on a variety of issues, ranging from science to politics. He was somewhat frustrated because his project was not going well and because of personal problems.

Before joining the laboratory, I had set my mind on working on the various DNA intermediates in retrovirus-infected virus cells because of the spectacular discovery of reverse transcriptase by Mizutani and Temin, and by Baltimore, in 1970 (Mizutani did not get the prize, Temin did). When I arrived in the laboratory, Bishop suggested that I should talk to all the postdoctoral fellows and technicians to familiarize myself with various projects. After several discussions, I made up my mind to work on DNA intermediates, as nobody else was actively pursuing that topic. Varmus himself was working on integration by network formation followed by reassociation kinetics. He advised me on various tissue culture and molecular biology techniques, and Nancy Quintrell, a research assistant, provided me with valuable information on preparing probes and so on.

After a week, I had a meeting with Bishop and Varmus, at which Varmus suggested that I should first start by preparing the *src* probe. He outlined the rationale, which was based on the original observation by Peter Duesberg and Peter Vogt that transformation-defective variants lack a sequence of about 1,000 to 1,500 nucleotides. It sounded to me very interesting and I therefore set out to do the experiments.

I prepared radiolabelled cDNA probes from wild-type virus and hybridized them to the 70S RNA from transformation-defective (td) virus. I began to notice differences in the extent of hybridization between them and therefore pursued this observation vigorously for three or four months. As my heart was set on doing experiments with viral DNA intermediates, I began those experiments simultaneously. In about two or three months, I

obtained evidence that the first steps of reverse transcription occur in the cytoplasm. We were all excited by what seemed to be a seminal observation, but I had to prove that the DNA we detected in the cytoplasm was not due to leakage from nuclei. After these initial observations, Varmus started enucleating the cells to show conclusively that DNA synthesis occurs in the cytoplasm.

In the next few months, we concentrated on this project, which resulted by the end of 1973 in the discovery of supercoiled DNA. As a result of this diversion, I had to slow down the work on *src*, and was only occasionally able to work on that project. One day in July 1973, Bishop came to me and said, "Ram, since your project on DNA synthesis is going so well, do you mind if Dominique continues this project; but I want to assure you that you are part of this project as well".

I readily accepted the proposal, since Stéhelin was (and is) a good friend, and his original project was not going well. I handed over my notebook to Stéhelin. He started working on this project at the end of July or August 1973, while I pursued the studies on DNA intermediates. By the end of 1973, we found supercoiled DNA, and the work on this was presented in 1974 at a symposium held at Rutgers University and at the Cold Spring Harbor meeting and later published in *Nature* in 1975.

I continued to attend the weekly meetings with Bishop, Varmus and Stéhelin until the middle of 1974, but discontinued later because of my own projects and also because of my intensive effort at job hunting. Stéhelin worked hard, and successfully prepared the *src* probe. Once the probe was defined, it was logical to evaluate it on all the DNAs available.

In my view, Bishop and Varmus deserve the Nobel prize. Several others such as Peter Duesberg, Peter Vogt, H. Hanafusa, Jeff Cooper and R. A. Weinberg could have been included, because the first three laid down fundamental work which made possible the oncogene work on retroviruses and the last two contributed to identifying cellular oncogenes not present in retroviruses.

In retrospect, it seems to me that if I had not obtained positive results, there would have been no oncogene project. In many laboratories, many students and research fellows begin work on new projects, but not many succeed. Initial failure of any project results, in general, in its abandonment. Very few continue on a project when several experiments fail. That was what happened to Stéhelin's first project and therefore, to my mind, fortuitous circumstances paved the way for his involvement in the oncogene project.

Therefore, as the first participant in the early work, in the 1970s, which led to the

award of the 1989 prize, I believe that the Nobel committee acted prudently in the selection of Bishop and Varmus. I hope that the Nobel committees will continue to base their decisions on scientific merit, ingenuity and the impact of discoveries and ignore the publicity and politics which develop following some discoveries, such as that of the AIDS virus, which is but one among many such discoveries and controversies of the past decade.

RAMAREDDY V. GUNTAKA

Department of Molecular Microbiology
and Immunology,
University of Missouri-Columbia,
Columbia, Missouri 65212, USA

SIR—Under the heading "Conduct unbecoming", *Nature*¹ says that "As all agree, Stéhelin was the main pair of hands behind the experiments that first showed that the oncogenes of tumour viruses are stolen and corrupted versions of genes from the cells. . .". The latter half of this statement is incorrect for the following reasons.

The first demonstration of the cellular origin of viral oncogenes was published from entirely different laboratories three years before the paper by Stéhelin *et al.*² appeared in 1976. Scolnick *et al.*¹⁰, cited in Stéhelin *et al.*'s 1976 paper, and Tsuchida, Gilden and Hatanaka⁴ observed in 1973 and 1974 respectively that the *ras* sequences, then called *src*, of Harvey and Kirsten sarcoma viruses were from cellular genes. The title of a paper by Scolnick and Parks in 1974 is "A second murine Type C virus with rat genetic information"³ and that of a paper by Tsuchida, Gilden and Hatanaka is "Sarcoma virus related RNA sequences in normal rat cells"⁴. The protocol of these experiments was exactly the same as that used later by Stéhelin *et al.* and so was the conceptual basis, namely to test Huebner's and Todaro's oncogene hypothesis of 1969⁵ with the then newly discovered viral oncogenes. The oncogene hypothesis postulated the existence of switched-off cancer genes in normal cells. The only technical distinction between the original experiments with the Harvey and Kirsten viruses and the later ones by Stéhelin *et al.* with the Rous sarcoma virus was that, in addition to sequences from the cell, the Harvey and Kirsten viruses had also 'stolen' sequences from an endogenous rat retrovirus. This was painstakingly and convincingly sorted out by the Scolnick group in subsequent years.

Further, there is no mention in Stéhelin *et al.*'s paper² that the sequences transduced had been 'corrupted' cellular sequences. Instead, these sequences were called viral homologs of cellular genes in this² and subsequent studies⁶. Indeed, on the basis of this homology, the cellular progenitors of viral *onc* genes were proposed to be switched-off cellular

oncogenes, abbreviated to this day as *c-oncs*, that would function as cancer genes by increased dosage⁶. Hence the term oncogene activation⁶. But subsequent work, mostly by others, has shown that viral *onc* genes and cellular progenitors have different functions because they have different structures⁷⁻⁹. So far, not a single cellular progenitor of a viral *onc* gene has been proved to be a cancer gene, except if it had been altered ('corrupted') by recombination with a retrovirus⁷⁻⁹. Yet it seems that the appeal of this hypothesis is the probable basis for the current Nobel prize.

All the points I make here had been made before the current controversy, first in *Nature* and later in other journals⁷⁻⁹ and have not so far been challenged.

PETER DUESBERG

University of California, Berkeley,
Department of Molecular and
Cell Biology,
Stanley Hall,
Berkeley, California 94720, USA

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Motive power

SIR—Virginia Trimble clearly establishes (*Nature* **342**, 11; 1989) that graduates of more prestigious universities publish for a longer professional period than those of other institutions. No one will want to squabble with this finding. But the conclusion that she draws, that "it still pays to go to the most prestigious graduate institution", is based on an assumption that is congenial to a physicist used to classes of identical objects. It is the assumption that the samples of students in the two kinds of institutions are equivalent and that their lifelong behaviour is the result of their institutional association. This ignores, however, the fact that only one in seven or even one in 10 of the applicants to a prestigious institution is accepted, while in less prestigious institutions the selection is far less severe.

One of the criteria on which this drastic selection is based is an indication of high motivation of the applicant. This criterion is of great importance because many studies have shown that high motivation, all else being equal, is usually more important for high achievement than mere intelligence. In other words, there is much to indicate that the continuing high moti-

vation of graduates from prestigious institutions is due to the fact that they represent a sample selected for high motivation.

This conclusion does not deny the additional factor of an intellectual climate in the prestigious institution that favours continuing productivity nor other aspects of the environment (such as lower teaching load) that also favour high productivity. Yet all the evidence indicates that continuing high motivation is not primarily the effect of institutional association.

ERNST MAYR

Museum of Comparative Zoology,
Harvard University,
Cambridge, Massachusetts 01138, USA

Nonrandom uses

SIR—The word "random" is sometimes used in *Nature* and other publications where another term such as "chaotic", "unpredictable", "uncertain", "arbitrary" or "undetermined" should be used. The use of "random" to describe a process, behaviour or physical system should be reserved for cases where an author can prove the system is random.

The primary definition of "random" is "proceeding, made, or occurring without definite aim, reason, or pattern"¹. "Apparently random fluctuations"² would be better expressed as "unpredictable fluctuations" as there are "structures" and "regularity".

When "random" is used to denote a selection process³ or simulation method, close attention must be paid to the implementation of the randomizing process. That the chaotic orbits of a three-body system would upon ejection of a member "randomize the spin orientation"⁴ is neither demonstrated in the paper nor an expected result of the ejection. Instead, the spin orientation is deterministic and yet unpredictable. The reason and pattern for the spin orientation are known; it is the limits of observation and the limits of computability that prohibit prediction.

In a statistical sense, "random" is "of or characterizing a process of selection in which each item of a set has an equal probability of being chosen¹ and is properly used in *Nature* **342**, 128 (1989) when speaking of a "random distribution of orientations" as a metric.

Even the use of "random" in statistical analysis and computer science must be viewed critically⁵. Computers are used to generate sequences representing random selections using deterministic algorithms. Some common computer randomization methods produce less than exemplary results. These algorithms produce reproducible sequences that have qualities that emulate "random" behaviour (if such a thing as random behaviour exists). These computer-generated sequences are better termed "pseudo-random".

If system history influences succeeding

states, then we cannot consider it random merely because we do not know the aim, reason or pattern. In dynamics we must carefully consider evidence such as power spectral distribution, trajectory, degrees of freedom, rate of divergence and dimensionality when branding a system "chaotic". The same burden of proof should apply to those who report a system to be "random".

THOMAS L. OCHS

US Bureau of Mines,
1450 Queen Avenue, SW,
Albany, Oregon 97321, USA

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Embryo research

SIR—Public attitudes to fertilization and embryology have been shown to be considerably pliable. This is well illustrated in the Warnock Report by the issue of artificial insemination by husband (AIH) and by donor (AID). The Archbishop of Canterbury in 1948 was highly critical of the practice of AID, though not of AIH, recommending that it should become a criminal offence. But no action was taken.

In 1960, the Feversham Committee, set up by the government to consider AI, reported; it considered that AIH was an acceptable form of treatment for some couples, but believed that most people within both society and the medical profession were opposed to the practice of AID. It concluded that AID was an undesirable practice, strongly to be discouraged. Since 1960, the practice of AID has continued to grow. In 1968, the then Minister for Health decided that AIH and AID should be available within the NHS if recommended on medical grounds.

I do not wish to discuss whether such a change has been for the better, but the history of attitudes towards AID illustrates how, in the absence of parliamentary restrictions, the views of a progressive minority may become widely adopted. Although the issues involved in *in vitro* fertilization are not the same, it might be argued that they are of sufficient importance that future changes on such matters as a time limit for experimentation should be subject to parliamentary review. Opinions such as "Why not start with a 14-day limit [on embryo research] imposed by regulation with the intention of relaxing that if the new authority can make a convincing case for doing so, and win public acceptance for its plans?" (*Nature* **342**, 461; 1989) fuel the fears of those opposed to any advance.

JONATHAN J. EW BANK

MRC Laboratory of Molecular Biology,
Hills Road, Cambridge CB2 2QH, UK