The 1975 Nobel Prize for Physiology or Medicine

The 1975 Nobel Prize for Physiology or Medicine was awarded to Renato Dulbecco, David Baltimore, and Howard Temin for their discoveries concerning the interaction between tumor viruses and the genetic material of the cell. The investigators were cited for providing the conceptual foundation and technology for examining a possible relationship between viruses and human cancer.

"It will be important not to be afraid of the complexities," Renato Dulbecco remarked, referring to cell growth control in his opening address at the Cold Spring Harbor symposium on tumor viruses in 1974. That the complexities of the interaction between tumor viruses and host cells can be faced squarely is in large part due to the contributions to the developing field of tumor virology made by Dulbecco and two of his former colleagues, Howard M. Temin and David Baltimore. For these contributions, the three scientists have been awarded the 1975 Nobel Prize for Physiology or Medicine.

Dulbecco's work with animal viruses began in the ambience of the group working on bacteriophage at the California Institute of Technology, Pasadena, where quantitative assays for virus growth and development had met with spectacular success. The need for similar assays in work with animal viruses was apparent to Dulbecco, and he developed the first plaque assay for an animal virus, Western equine encephalitis virus, in 1952. Shortly thereafter, he was joined by Marguerite Vogt who was to be his colleague and close collaborator for 20 years.

Dulbecco and Vogt concentrated mainly on poliovirus, another of the small RNA viruses, for the next 6 years, perfecting techniques for studying virus growth in tissue culture. Dulbecco turned to DNA viruses in 1959, choosing to work with the tumor virus, polyoma. Polyoma was so named by S. E. Stewart and B. Eddy because of its ability to induce a variety of tumors in mice. The small size of this DNA virus attracted Dulbecco, who hoped to use it to analyze genetic recombination in animal viruses. Dulbecco and G. Freeman developed a plaque assay for polyoma in 1959. In the course of studying polyoma-infected cells in culture, Dulbecco, Freeman, and Vogt noticed that cells in the infected cultures grew differently from uninfected cells. The "transformed" cells showed an altered morphology and growth pattern. Dulbecco and Vogt systematically characterized the changes in cell growth patterns occurring after polyoma infection, and showed that cells transformed in culture by virus infection are tumorigenic in animals. Their discovery of cell transformation was a major step forward. It provided an in vitro experimental system for analyzing the changes in growth regulation that occur when a cell becomes malignant, and opened the way for biochemical analysis of cells infected and transformed by DNA tumor viruses.

In 1963 Dulbecco and Vogt moved to the newly formed Salk Institute in La Jolla, California, where Dulbecco established a research group to study DNA tumor viruses and cell growth regulation. Under Dulbecco's leadership, this group made a series of important contributions to the development of DNA tumor virology during the 1960's; it served as a training ground for younger scientists, developed collaborations with others in the field, and produced a series of discoveries that helped to define the nature of the interaction between DNA tumor viruses and host cells.

During this time, research in DNA tumor virology grew rapidly, and the lines of investigation pursued by the group in La Jolla reflected the progress of the field as a whole. Polyoma and simian virus 40 (SV40) were found to cause a wide variety of regulatory changes in infected cells, including the activation of cellular DNA synthesis and the production of virus-specific antigens. The persistence of virus-specific antigens in transformed cells suggested that viral information might persist too, and evidence gradually accumulated to indicate that viral DNA was incorporated into the cellular genome. Techniques were developed to show the presence of viral DNA and virus-specific RNA by molecular hybridization. In some cases, infectious virus could be recovered from transformed cells. The viral DNA sequences were found in close association with cellular DNA, probably covalently integrated into cellular chromosomes.

The regulation of viral gene expression was studied intensively. Transcription of viral information, and synthesis of virus-coded proteins, is restricted to about one-half of the viral genome in transformed cells, corresponding to the viral information expressed early during lytic infection. These observations focused attention on the early region of the viral genome, coding for proteins with a molecular size of about 100,000 daltons, as the source of proteins involved in cell transformation. Studies with temperature-sensitive mutants showed that viral gene expression was required for cell transformation and was required to produce a variety of phenotypic changes in the infected cell.

The picture emerging from these studies of cell transformation by DNA tumor viruses is that the DNA of the infecting virus becomes established as a hereditary element in the transformed cell, contributing genetic information for the synthesis of proteins which affect cell growth control. The changes in control of cell growth are progressive, involving changes in many cellular properties. The cell surface appears to be a key component in regulation of cell growth.

In 1972, Dulbecco left California to live in England, where he is assistant director for research at the Imperial Cancer Research Fund Laboratories in London. The role of viral gene products in control of cell growth control is a major unanswered question in tumor virology, and Dulbecco and his colleagues are now engaged in attempts to isolate and characterize the viral proteins involved in cell transformation.

DNA tumor viruses have become basic tools for studying the molecular biology of

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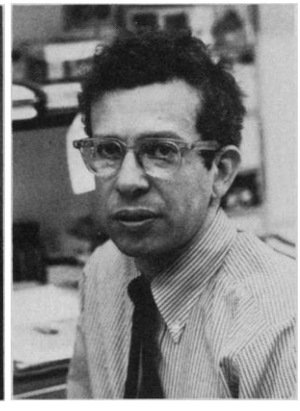
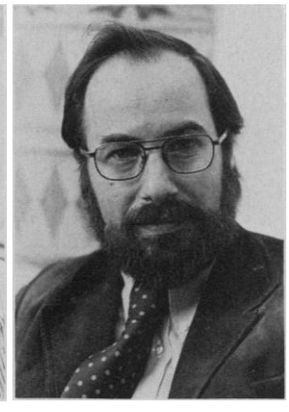
Renato Dulbecco



Howard M. Temin



David Baltimore

would make a profit of zero, in the sense that the price of the commodity at its destination would equal the price at its origin plus the unit shipping cost along that route. Moreover, the routes not being used would all make a profit less than or equal to zero. This permitted him to make the fertile suggestion that once the correct prices were known, the optimal selection of routes could be done in a decentralized fashion by managers who had in mind their own private considerations of profit maximization.

In 1944 Koopmans became a member of the Cowles Commission for Research in Economics, then located at the University of Chicago. Within a short period of time, Koopmans and his associates made the Cowles Commission into one of the major centers for the study of the optimal allocation of resources and its applications to a wide variety of economic problems.

In the late 1940's Koopmans extended his observation about the relationship between prices and optimality to the general activity analysis model. He demonstrated that any efficient production plan for such a model (a plan for which no alternative existed using less inputs and providing a greater output) would be associated with a vector of prices. The prices would yield a profit of zero for the activities composing the plan and a profit less than or equal to zero for all remaining activities. The insights about the decentralization of economic activity, in response to considerations of profit, were now available, not only for the transportation problem but for the functioning of an economic system in its entirety.

Many other remarkable innovations in economics were taking place at the same time. The modern study of the general equilibrium model, in which the theory of production is united with a description of consumer preferences, was inaugurated by Arrow, Debreu, and others; game theory, initiated by von Neumann and Morgenstern, made its appearance; the statistical estimation of complex economic relationships began to be studied; Arrow's book *Social Choice and Individual Values* was in the making; and Dantzig was developing the simplex method for linear programming problems which, in conjunction with the modern electronic computer, was to transform the activity analysis model into a tool for the solution of concrete economic problems.

But unknown to Western economists a corresponding development was taking place in the Soviet Union. In 1939 Leonid V. Kantorovich, the corecipient of the Nobel prize, presented a paper to a Leningrad seminar, whose contents were not available to colleagues in the West until some 20 years had passed. The paper, subsequently published under the title "Mathematical methods of organizing and planning production," provided its own formulation of the activity analysis model—somewhat different from that presented in the West—and outlined a computational technique for solving related linear programming problems. I find it difficult to appreciate the intellectual milieu in which the paper was written other than to see it as a response to specific practical questions addressed to its author. Kantorovich had been a pure mathematician whose previous publications gave no indication of an exposure to economic reasoning. It is all the more astonishing that, in the 1939 paper, the problem of the allocation of resources is treated not only from a mathematician's point of view but with a realization of the role played by prices in reaching an optimal decision. This paper and subsequent work by Kantorovich and his colleagues provided the base for the vigorous school of mathematical economics in the Soviet Union, which finally made its emergence in the late 1950's.

I have referred to linear programming without being explicit about the meaning of this term. Linear programming problems arise when the technical knowledge summarized by an activity analysis model is confronted with a given stock of factors of production and a specific objective to be maximized. A linear programming problem involves finding a nonnegative vector which satisfies a series of linear inequalities and which maximizes a given linear function. The first general formulation of these problems in the West was provided in 1947 by George B. Dantzig, currently Professor of Operations Research at Stanford University. At that time Dantzig and others were employed by the U.S. Air Force in the development of scientific programming techniques. Dantzig's concerns were with the explicit numerical solution of linear programming problems, and in the summer of that year he introduced the computational technique known as the simplex method. It is a remarkably effective algorithm, converging to the optimal solution in a relatively small number of iterations, even for problems of substantial size. Since that time Dantzig has remained the central figure in the development of a wide variety of mathematical programming methods and their application to problems of practical importance.

In my judgment, a computational technique which extends the range of applicability of economic theory—as the simplex method has done—is in itself a theoretical innovation of the highest order. This is particularly true in view of the close analogy, often cited by economists, between market mechanisms and formal mathematical techniques of optimization.

The techniques of activity analysis exemplify the pure theory of decision-making, and, as such, they are remarkably indifferent to economic institutions and organizational forms. For some economists, this is a deficiency of the theory of optimum allocation of resources: the forms in which economic activity is organized do matter. But on the other hand, one of the great achievements of this methodological revolution has been the continued dialogue—free of ideological overtones—between economists of the East and the West. This has been an event of considerable significance, and not only for economic reasons.

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mammalian cells. A great deal is known about their DNA structure, function, and replication. Dulbecco's original goal of using a small DNA animal virus to study genetic processes is well on the way to realization. The role of these viruses in cell growth control is much less clear. Control of cell growth is itself a complex and subtle process and will require cooperative efforts from many different directions in order to be understood.

Howard Temin and David Baltimore were led to their simultaneous but independent discoveries of RNA-dependent DNA synthesis by RNA tumor viruses (reverse transcription) from quite different directions. Temin studied Rous sarcoma virus (RSV) when he was a graduate student at Caltech, working with Harry Rubin in Dulbecco's laboratory. In 1958 Temin and Rubin developed the first reproducible assay in vitro for a tumor virus, the focus-forming unit assay for RSV in chick embryo fibroblasts.

Temin continued to work with RSV after moving to Wisconsin in 1960, and was intrigued with the observations that inhibition of DNA synthesis, and inhibition of DNA-dependent RNA synthe-

sis, would block RSV infection, even though the genome of RSV was a single-stranded RNA. To account for these observations, Temin proposed in 1964 that a DNA intermediate is involved in RSV infection. This "provirus hypothesis" envisioned that after infection a DNA provirus was synthesized which contained all of the genetic information of the RNA viral genome. Progeny viral RNA would be synthesized from the provirus, thereby accounting for the sensitivity of infection to inhibitors of both DNA synthesis and DNA-dependent RNA synthesis. If the provirus were integrated into the cellular genome, the stable inheritance of RSV transformation could be explained.

The provirus hypothesis did not achieve instant popularity. The evidence for the idea was indirect, and much of it relied on studies in which inhibitors, which were widely suspected of producing artifacts, were used. Moreover, the hypothesis conflicted with the scheme that had become known as the central dogma of molecular biology. The dogma specified that the information of DNA was first transcribed into RNA and then into proteins. People had come to expect that information flow would not occur in the reverse direction, that is, from RNA to DNA. However, Temin and John Bader independently accumulated additional evidence over the next 5 years implicating DNA synthesis in RSV infection, but made few inroads into the skepticism of their colleagues. Then, in 1970, Temin and Satoshi Mizutani did an experiment that changed the climate of opinion dramatically. They showed that the virions of RSV contain an enzyme that can transcribe the single-stranded virion RNA into DNA. This evidence, obtained simultaneously by Baltimore, using Rauscher murine leukemia virus and RSV, provided a mechanism for the formation of a DNA intermediate during RNA tumor virus infection and transformation, and clothed Temin's original hypothesis in respectability.

David Baltimore was trained as an animal virologist, working with Richard Franklin and James Darnell at the Rockefeller Institute and at the Massachusetts Institute of Technology. In 1965 he moved to La Jolla to join the virology group at the Salk Institute with Dulbecco. There he studied the mechanism of replication of poliovirus, making rapid progress in characterizing the replication of the viral RNA and the synthesis of the viral proteins. In 1967 Alice Huang joined the laboratory as a postdoctoral fellow. She had studied with Robert Wagner, doing much of the pioneering work on vesicular stomatitis virus (VSV) and its defective interfering particles.

In 1968 Baltimore moved to MIT, and Huang went with him to Boston, where they were married. Baltimore continued his work with poliovirus, and Huang resumed her work with VSV. They were led to consider the problems facing an RNA virus whose genome is complementary to its messenger RNA. In order to replicate, such a virus would have to use a cellular RNA-dependent RNA polymerase (for which there was no evidence) or would have to contain a virus-coded polymerase in its virion. Baltimore, Huang, and M. Stampfer showed that VSV particles did indeed contain an RNA-dependent RNA polymerase. Baltimore, with his broad interests in the biology of animal viruses, immediately decided to test for the presence of a polymerase in the virions of RNA tumor viruses. Because his laboratory was not equipped to grow large quantities of RNA tumor viruses, he used a sample of Rauscher murine leukemia virus provided by the National Cancer Institute and demonstrated the presence of an RNA-dependent DNA polymerase in these virions and in RSV.

The RNA-dependent DNA polymerases of RNA tumor viruses have quickly become standard tools for cell biologists. They are used to prepare radioactive DNA probes to detect viral genetic information in normal and malignant cells. They are used to prepare DNA copies of messenger RNA's which can be isolated and purified. Whether they play a role in cellular differentiation or development is not clear, but their role in the life cycle of RNA tumor viruses has been firmly established.

The awarding of the Nobel Prize to Dulbecco, Temin, and Baltimore marks the convergence of lines of research which at one time were thought to be quite separate. It now seems clear that the DNA tumor viruses and the RNA tumor viruses operate, at least in part, by a common pathway. They become part of the genetic material of the cells they transform. To what degree they resemble each other in the mechanisms by which they affect cell growth regulation is a fascinating question for the future.

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Articles on the Nobel Prize for Chemistry and the Nobel Prize for Physics will appear in subsequent issues of Science.