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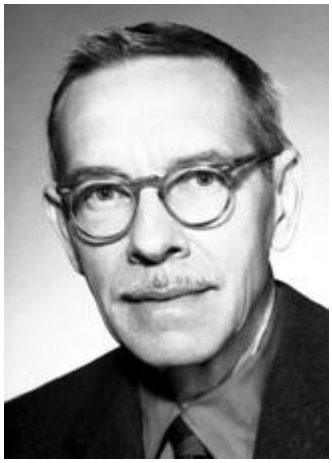
Nobel Prize in Medicines 1969


Max Delbrück


Alfred D. Hershey


Salvador E. Luria

The Nobel Prize in Physiology or Medicine 1969 was awarded jointly to Max Delbrück, Alfred D. Hershey and Salvador E. Luria "for their discoveries concerning the replication mechanism and the genetic structure of viruses"

Around 1940 Delbrück, Hershey and Luria became interested in bacteriophage, a type of virus that infects bacteria, rather than ordinary cells. They were trying to find a living system as simple as possible, on which to study with hope of success, fundamental life processes, first of all self-replication. Bacteriophage soon revealed itself to be an object of choice for such research. They worked out rigorous quantitative methods and this turned bacteriophage research into an exact science. They synchronized virus multiplication and were thus able to follow in detail the various phases in the process. They studied what happened in single cells and analyzed their results with advanced statistical methods. They made a series of fundamental discoveries, of which the following will be mentioned.

As a result of infection, both virus and cell undergo drastic changes. The so-called cell-virus-complex behaves as an essentially new system. The chemical activities of the cell

are reprogrammed. The virus loses its individuality and enters an "eclipse" or "dark" phase, during which it can no longer be identified as a particle. The metabolic activities which it releases can lead in a matter of minutes to the formation of hundreds of new virus particles.

The virus particle consists principally of nucleic acid surrounded by a protein shell. At infection the nucleic acid is injected by a simple but extremely efficient mechanism into the cell, while the protein shell remains outside. The role of nucleic acid as the carrier of the genetic information of the virus was thus demonstrated. The discovery of numerous genetic variants of the virus showed that the latter contained more than a single gene. Soon after genetic recombination was discovered to take place: two virus particles simultaneously infecting the same cell can exchange parts of their strings of genes and give origin to hybrid forms. This phenomenon made possible a detailed analysis of the genetic structure of the virus. Thanks to the short reproduction time of the virus and the large number of progeny virus obtained, bacteriophage work, in a matter of hours, can yield information that with other virus material might require months or years.

The work of Delbrück, Hershey and Luria has had a great impact on biology in general. Bacteriophages have served and continue to serve as models for the more complicated and less approachable systems represented by animal and human cells. Delbrück, Hershey and Luria have set the solid foundations on which modern molecular biology rests. Without their contributions the explosive development of this field would have been hardly possible. From the medical point of view, the discoveries for which the award is now given first of all imply a deeper insight into the nature of viruses and of virus diseases. Indirectly they also bring about an increased understanding of the mechanism of inheritance and of those mechanisms that control the development growth and function of tissues and organs. Over the years our debt of gratitude to the three leading figures of bacteriophage research has continually increased.

Delbrück was trained as a physicist, but soon became interested in biological problems. Already in 1933, in Berlin, he had joined a research group that was

experimenting on the production of mutations in fruit-flies with different kinds of radiations. This collaboration led to a quantum-mechanical model of the gene, permitting, for example, estimations of gene size. But there was little promise of further advance in the field as long as complex organisms were used as experimental material. Simpler biological systems had to be found.

A few years later, in the United States, after meeting a colleague who was working with bacteriophage, he realized that this might be an ideal material for the experimental attack of the most fundamental biological problems, self-replication and mutation.

At about the same time, Luria, a research minded physician, who had just come to the United States from Italy, was using bacteriophages in radiobiological experiments of the kind that the Berlin group had performed on fruit-flies. In the United States, Delbrück and Luria became well acquainted with each other and collaborated on several occasions. Together they gave new impetus to research on bacteriophages.

Bacteriophages are a group of viruses that infect bacteria rather than ordinary cells. They can multiply very rapidly and in very large numbers. They are not pathogenic to man, hence can be handled with rather simple bacteriological methods. Discovered as early as 1915, bacteriophages had been the object of much work over the years, but few results of biological or medical importance had come from it. Delbrück and Luria introduced into this field genetic concepts and rigorous quantitative methods.

Between 1940 and 1945 they established the main outlines of bacteriophage multiplication (duration of the infectious process, number of progeny bacteriophages produced by an infected bacterium, the various stages of the infectious process, etc.) They introduced criteria for distinguishing mutation from other modifications in both bacteriophage and bacteria. They began to explore the interactions taking place when virus particles of two different kinds infect the same bacterium.

Their work attracted the attention of Hershey, a microbiological chemist, who had already used bacteriophages for many years as antigens in his studies of immunological reactions. At this time a very fruitful collaboration began to develop between Delbrück,

Hershey and Luria, and their laboratories. No joint research program was implied. Rather, this collaboration was based on a free exchange of information and material, on avoiding duplication of efforts, and on refraining from any unproductive form of scientific competition. A school, the so-called "phage group" informally grew up around Delbrück, Hershey and Luria, with a geographic center at the Biological Laboratory in Cold Spring Harbor, where informal research conferences were often held.

In 1946 Hershey demonstrated the independence of different mutation types occurring in the same virus: this was the first indication that a virus may contain more than one gene. In the same year Delbrück discovered an unexpected genetic interaction between viruses infecting the same cell. Hershey further advanced this work. He demonstrated that the phenomenon was due to genetic recombination and that it could be used to construct the genetic map of virus. Luria was able to support this interpretation with experiments in which genetic damage caused by radiation in bacteriophages could be repaired by gene exchange following infection of the same host bacterium with several damaged virus particles. These findings opened tremendous possibilities of analyses of the structure of genetic material.

It was then known from the observations of several other investigators that bacteriophage particles were made of protein and nucleic acid, with the nucleic acid located inside the particles and the protein outside. It had also been found that relatively simple manipulations could split the two components. Hershey posed the question of whether a similar splitting took place in the course of infection. By using radioactive label in the protein or in the nucleic acid, he was able to show (1952) that only the nucleic acid of the virus entered the bacterium, hence was sufficient for the complete reproduction of the bacteriophage. The experiment demonstrated that the nucleic acid of these viruses was their genetic material.

Hershey continued the work with a very thorough analysis of the metabolic processes taking place in the bacterium following entry of the virus nucleic acid. He succeeded in establishing the basic picture of the infectious process of a bacteriophage in

biochemical terms. In the course of this work he uncovered the very first indication of the special nucleic acid fraction (messenger RNA) that is now known to act as information carrier between genetic material and protein.

In later times Delbrück has made theoretical contributions to the problem of how nucleic acid replicates, although his main research interest has shifted from genetics to physiology. Luria has investigated phenomena of conversion, in which a bacteriophage carried by a bacterium in a semi-permanent association produces certain changes in the properties of the bacterium. These systems are used as models for similar interactions in animal cells, where association with a virus can cause the cell to become cancer-like. Hershey has developed new techniques for the study of nucleic acid molecules. He has demonstrated the interconversion of a linear nucleic acid molecule to a ring-shaped one.

During the last 15 years the work on bacteriophage has had a tremendous impact on virology, and has supplied material and techniques which have been essential to the progress of molecular biology. The basic sequence first demonstrated in bactoriophage reproduction: splitting of the virus particle into nucleic acid and protein, multiplication of the nucleic acid, synthesis of specific viral protein, and reconstitution of progeny virus particles from the new nucleic acid and the new protein is now generally accepted as the basic pattern of reproduction of all viruses.

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