ISSN:2249-5347
IJSID
International Journal of Science Innovations and Discoveries
An International peer Review Journal for Science

Nobel Prize in Medicines 1965


François Jacob


André Lwoff


Jacques Monod

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The 1965 Nobel Prize in Physiology or Medicine is shared by Professors Jacob, Lwoff and Monod for «discoveries concerning the genetic regulation of enzyme and virus synthesis».

This particular sphere of research is by no means easy. I heard one of the prize winners, Professor Jacob, forewarn an audience of specialists more or less as follows: «In describing genetic mechanisms, there is a choice between being inexact and incomprehensible». In making this presentation, I shall try to be as inexact as conscience permits.

It has become progressively more apparent that the answer to what has hitherto been romantically termed the secret of life must be sought in the mechanism of action and in the structure of the hereditary material, the genes. This central field of research has naturally been approached from the periphery and in stages. Only in recent years has it

been possible to make a serious attack on these fundamental problems. Several previous Nobel Prize holders: Beadle, Tatum, Crick, Watson, Wilkins, Kornberg andOchoa have worked in this sphere of research and have formulated certain basic proposals which have enabled the French scholars to continue their efforts. It has been established that one of the principal functions of genes must be to determine the nature and number of enzymes within the cell, the chemical apparatus which controls all the reactions by which the cellular material is formed and the energy necessary for various life processes is released. There is thus a particular gene for each specific enzyme.

In addition, some light has been thrown on the chemical structure of genes. In principle, they have the form of a long double chain consisting of four different components, which can be designated by the letters a, c, g, and t, and with the property of forming pairs with each other. An «a» in one of the chains has to be matched by a «t» in the other, a «g» only by a «c». However, they can be linked along the length of the chain in any order whatsoever, so that the number of possible combinations is virtually unlimited. A chain of genes contains from several hundreds to many thousands of units; such structures can easily carry the specific patterns for the million or more genes which it is estimated that a cell may have.

This model of the genes represents a coded message containing two types of information. If the double chain of a gene is split lengthwise and each half acquires a new partner, then the final result is two double chains identical to the original gene. The model thus contains information relative to the actual structure of the gene, which permits multiplication, in its turn a condition of heredity. When a cell divides, each daughter cell receives an exact copy of the parent gene. The structure of the double chain ensures the stability and permanence required by hereditary material.

But the model can also be read in another way. Along the length of the chain, the letters are grouped in threes in coded words. An alphabet of four letters allows the formation of more than 30 different words and the sequence in the gene of such words provides the structural information for an enzyme or some other protein. Proteins are also

chain molecules built up from twenty or so different types of building blocks. To each of these building blocks there corresponds a chemical code word of three letters. The gene thus contains information on the number, nature, and order of the building blocks in a particular protein.

Thus it was already clear that the hereditary blueprint contained the collective structural information for all substances necessary for the functions of the living cell. It was not known how the genetic information was put into effect or transformed into chemical activity. As to the function of the genes, it was thought that they participated in a sort of procreative act when the new cell came into being, producing new substances necessary for the life of the cell, but subsequently lying dormant until the next cell division. It was presumed that the structure and formation of the chemical apparatus determined in this way defined all the regulatory mechanisms necessary for the cell's ability to adapt to changes in the environment and to respond in an adequate manner to stimuli of different types.

To begin with, the group of French workers were able to demonstrate how the structural information of the genes was used chemically. During a process resembling gene multiplication an exact copy of the genetic code is produced, termed a messenger. The latter is then incorporated into the chemical «workshop» of the cell and wound like magnetic tape onto a spool. For each word arriving on the spool, a constructional unit is attracted, which carries a complement to this word and attaches itself there just like a piece of jigsaw puzzle. The building blocks of a protein are selected in this way one by one, aligned, and joined together to form a protein with the appropriate structure.

The messenger substance is, however, short-lived. The tape lasts only for a few recordings. The enzymes are also used up in a similar way. For the cell to maintain its activity, it is thus necessary to have an uninterrupted production of the messenger material, that is to say continuous activity of the corresponding gene.

However, cells can adapt themselves to different external conditions. Thus there must exist some mechanisms controlling the activity of the genes. The research into the

nature of these mechanisms is a remarkable achievement which has opened the way for the possible explanation of a series of hitherto mysterious biological phenomena. The discovery of a previously unknown class, the operator genes, which control the structural genes, marks a major breakthrough.

There are two types of operator genes. One type releases chemical signals, which are perceived by a second, receptor, type. The latter controls in its turn one or more structural genes. As long as the signals are being received the receptor remains blocked and the structural genes are inactive. Certain substances coming from outside or formed within the cell can, however, influence the chemical signals in a specific manner, changing their character so that they can no longer influence the receptor. The latter is unblocked and activates the structural genes; messenger material is produced and the synthesis of enzymes or another protein commences.

Control of gene activity is thus of a negative nature; the structural genes are only active if the repressor signals do not arrive. One can speak here of chemical control circuits similar in many ways to electrical circuits, for example in a television set. In the same way, they can be interconnected or arranged in a series to form complicated systems.

With the aid of such control circuits, the free living monocellular organism can produce enzymes when required, or interrupt chemical reactions if they are likely to cause damage; an excitatory stimulus can provoke movement, flight or attack, depending on the nature of the excitation. With such mechanisms it is possible to direct the development of cells into more complicated structures. It is particularly interesting to note that the activity of viruses is controlled, in principle, in the same manner.

Bacteriophages contain a genetic control circuit complete with emitter, receptor, and structural genes. While chemical signals are being sent and received, the virus remains inactive. When incorporated into a cell, it behaves like a normal component of the cell, and can confer on it new properties which may improve its chances of survival in the struggle for existence. However, if the signals are interrupted, the virus is activated, starts to grow rapidly and soon kills the host cell. There is considerable evidence for the view that certain

types of tumor virus are incorporated into a normal cell in the same way, thus transforming it into a tumour cell.

We are easily inclined to hold an exaggerated opinion of ourselves in this era of advanced technology. Thus, we are justified in having a great admiration for the achievements in electronics, where, for example, the attempts at miniaturization to reduce component size, to lower the weight, and reduce the volume of apparatus have enabled a rapid development of space science. However, we should bear in mind that, millions of years ago, nature perfected systems far surpassing all that the inventive genius of man has been able to conceive hitherto. A single living cell, measuring several thousandths of a millimetre, contains hundreds of thousands of chemical control circuits, exactly harmonized and functioning infallibly. It is hardly possible to improve on miniaturization further; we are dealing here with a level where the components are single molecules. The group of French workers has opened up a field of research which in the truest sense of the word can be described as molecular biology.

Lwoff represents microbiology, Monod biochemistry, and Jacob cellular genetics. Their decisive discovery would not have been possible without competence and technical knowledge in all these fields, nor without intimate cooperation between the three researchers. But the mystery of life is not resolved simply with knowledge and technical skill. One must also have a gift for observation, a logical intellect, a faculty for the synthesis of ideas, a degree of imagination, and scientific intuition, qualities with which the three workers are liberally endowed.

Research in this field has not yet yielded results that can be used in practice. However, the discoveries have given a strong impetus to research in all domains of biology with far-reaching effects spreading out like ripples in the water. Now that we know the nature of such mechanisms, we have the possibility of learning to master them, with all the consequences which that will surely entail for practical medicine.

François Jacob, André Lwoff, Jacques Monod. Thanks to your technically unimpeachable experiments and your ingenious and logical deductions, you have gained a

more intimate familiarity with the nature of vital functions than anyone before you has done. Action, coordination, adaptation, variation - these are the most striking manifestations of living matter. By placing more emphasis on dynamic activity and mechanisms than on structure, you have laid the foundations for the science of molecular biology in the true sense of the term. In the name of the Caroline Institute, I ask you to accept our admiration and our most sincere congratulations. Finally, I invite you to come down from the platform to receive the prize from His Majesty the King.

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http://www.nobelprize.org/nobel_prizes/medicine/laureates/1965/press.html